



91 annual report

Division Of

Cancer Etiology

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ANNUAL REPORT
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1990 through September 30, 1991

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ANNUAL REPORT OF
THE EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1990 through September 30, 1991

The Epidemiology and Biostatistics Program is the focus within the Institute for epidemiologic and biostatistical research in cancer etiology. The Program is responsible for intramural, collaborative, and grant-supported investigations into the distribution, causes, and natural history of cancer, as well as the means for preventing cancer. The Program employs comprehensive approaches in epidemiologic investigations that cover the gamut of environmental and host determinants of cancer. The Program also conducts and supports the development of new and innovative methodologic approaches in epidemiology and biostatistics, multidisciplinary investigations, and biostatistical and mathematical research on carcinogenic mechanisms and risk assessment.

Dr. Joseph F. Fraumeni, Jr. continued to direct the Program as the Associate Director for Epidemiology and Biostatistics. The five operational components of the Program remain the Biostatistics Branch (Chief, Dr. William J. Blot), the Environmental Epidemiology Branch (Chief, Dr. Robert N. Hoover), the Clinical Epidemiology Branch (Chief, Dr. Robert W. Miller), the Radiation Epidemiology Branch (Chief, Dr. John D. Boice, Jr.), and the Extramural Programs Branch (Chief, Dr. G. Iris Ostrom). The research and other scientific activities of each Branch are described in the sections following this report, which focuses on the orientation, highlights, and direction of the overall Program.

INTRAMURAL RESEARCH

Case-control and cohort studies continued to be the primary methodologic approaches for evaluating key hypotheses in cancer etiology. Studies were initiated when high-risk communities were identified from cancer mortality maps, major hypotheses were testable, or special resources became available. Biological specimens were often collected and laboratory assays performed to clarify exposures, susceptibility states, preclinical responses, and mechanisms of carcinogenesis. Special attention continued to be given to gender-specific cancers, as well as to those cancers rising over time or occurring excessively among minority populations.

Descriptive studies continued to examine geographic variation and clustering of cancer, and to relate these cancer patterns to demographic and exposure characteristics of the affected populations. Published this year was an updated atlas of maps illustrating cancer mortality trends from 1950-1980 among nonwhite populations. The atlas serves as a companion volume to a similar publication of mortality trends among whites. As noted for whites, the mortality patterns for most sites among nonwhites showed increasing geographic uniformity over time. Noteworthy exceptions to this pattern include the emergence in the 1970's of high rates for prostate cancer among black men in the South Atlantic states, rising rates of stomach cancer among

Native Americans in the Southwest, and limited declines in cervical cancer among black women in the Southeast.

Lung cancer incidence patterns from 1969 through 1986 were investigated by age, race, sex, and histologic type. The patterns were best described by birth cohort, with the rise and fall in squamous cell cancer rates preceding those for small cell and adenocarcinoma of the lung by 10 to 20 years within each race-sex group. This histology-specific pattern of changing rates by birth cohort occurred first for white males followed successively by black males, white females, and black females. Overall, the rates for squamous cell carcinoma in both sexes and for adenocarcinoma among men were substantially higher for blacks, whereas no racial disparity was seen for small cell carcinoma.

The possible carcinogenicity of fluoride compounds added to drinking water supplies was suggested by a recent animal experiment. This concern prompted an evaluation of 36 years of U.S. cancer mortality and 15 years of cancer incidence data in relation to the fluoridation status of drinking water supplies on a county-by-county basis. Based on results of the animal study, osteosarcomas of the bone were singled out for detailed analysis. No consistent evidence was found for a relationship between any malignancy and the pattern of fluoridation, and no trends in bone cancer or osteosarcoma incidence were correlated with the intake of fluoridated drinking water.

Tobacco and Alcohol: Research continued to define the roles of tobacco and alcohol on the risk of various cancers. Analyses of a 26-year follow-up of 250,000 U.S. veterans found dose-response relationships for cigarette smoking and myeloid leukemia and cancers of the stomach, prostate, kidney, and liver. Similarly, in a 20-year follow-up of almost 18,000 men from the upper midwest and northeast regions of the United States, dose-response relationships for cigarette smoking were identified for prostate cancer and lymphatic and unspecified leukemias. In a large-scale case-control study conducted in Los Angeles, Iowa, and New Jersey, cigarette smoking was found to account for almost three out of four cancers of the renal pelvis and ureter.

A large-scale case-control study revealed a 35-fold excess risk of oral cancer following heavy use of tobacco and alcoholic beverages. In addition, an increased risk of oral cancer was associated with the regular use of mouthwash with high (>25%) alcohol content; the risk increasing in proportion to the duration and frequency of mouthwash use. This finding suggests that alcohol may produce a carcinogenic effect through topical mechanisms.

Occupation: Exposures in the workplace are often heavier and more prolonged than those typically encountered by the general public, so that epidemiologic studies of workers offer unique opportunities to identify environmental causes of cancer. A number of recent investigations have focused on cancer risks associated with agricultural pesticide exposure. In a population-based case-control study in Nebraska, farmers using the phenoxyacetic acid herbicide, 2,4-D, experienced an elevated risk of non-Hodgkin's lymphoma (NHL), consistent with findings from an earlier study in Kansas. In addition, farmers who used organophosphate insecticides showed a twofold risk of NHL, which was independent of the risk from exposure to 2,4-D.

A case-control study of leukemia in Iowa and Minnesota revealed elevated risks among farmers, particularly if they used insecticides on animals. Risks of over twofold occurred from the use of various of insecticides, including carbaryl, coumaphos, dichlorvos, famphur, methoxychlor, nicotine, pyrethrins, and toxaphene. The risk of leukemia from the use of insecticides on crops was generally lower, possibly because of lower exposures.

A number of studies are underway to clarify cancer risks and to identify specific carcinogenic exposures in the agricultural environment. For example, case-control studies in Nebraska will assess the role of agricultural factors, including pesticides, in cancers of the lymphatic and hematopoietic system, brain and stomach. In addition, studies of pesticide applicators are being carried out.

Cancer risks from exposure to formaldehyde, an animal carcinogen, were evaluated in studies of industrial and professional workers. An excess of lung cancer among workers in formaldehyde-using industries was confined to those employed in formaldehyde resin and molding compound operations. In this group, the risk rose with duration of exposure to melamine, urea, phenol, and wood dust.

In a large proportionate mortality study of embalmers and funeral directors, a significant excess of lymphatic and hematopoietic cancers was observed among blacks and whites. An excess of nasopharyngeal cancer was also noted for the first time, consistent with the excess risk seen among industrial workers exposed to formaldehyde. An investigation, which includes a case-control interview component plus environmental and biologic monitoring, is underway to further evaluate cancer risks among embalmers.

In other studies, excesses of NHL and multiple myeloma were observed in a cohort employed at an aircraft maintenance facility, where a variety of organic solvents are used. These excesses are continuing to be evaluated in an extended follow-up of the cohort. Lung cancer was found to be elevated in silicotic workers employed in dusty trades in North Carolina. A large cohort study of silica-exposed workers in China should clarify the role of this mineral in occupationally-related lung cancer. In another study in China, follow-up of about 100,000 workers exposed to benzene will allow better estimates of the benzene-leukemia dose-response relationship and assess whether benzene causes other cancers. A follow-up study of nearly 30,000 tin miners and smelter workers in Yunnan province is assessing interactions between inorganic arsenic and radon, as well as examining time-related factors in cancer induction.

Efforts continued to evaluate and improve industrial hygiene and epidemiologic methods used in occupational studies. One project focused on the effects of exposure misclassification on risk estimates. Papers presented at an international workshop on retrospective exposure assessment, sponsored by NCI and the National Institute for Occupational Safety and Health (NIOSH), will be published in a special volume of *Applied Occupational and Environmental Health*.

Radiation: Populations exposed to ionizing radiation are studied to clarify cancer risks associated with low-dose exposures. This year, a variety of scientific and public health concerns were addressed, and special efforts were

made to apply laboratory approaches to detect genetic and other mechanisms that increase susceptibility to radiation-induced cancers.

In a study of populations living near nuclear facilities in the United States, excesses were not found for childhood leukemia or other cancers, in contrast to findings from the United Kingdom. Risks were slightly higher before the facilities began operations than afterward, providing little evidence that environmental releases of radiation influenced mortality rates in these areas.

New risk models, taking into account population mobility and occupancy, suggest that indoor radon may be less of a public health hazard than previously estimated. No association with levels of indoor radon was found for lung cancer in a case-control study of women in China, and a modest association seen among Swedish women disappeared when adjusted for occupancy. These results suggest that models for extrapolating risks from high exposures, based on miner data, to low-level exposures should be viewed cautiously. An ongoing study in Missouri, which includes innovative approaches to dosimetry, should provide new insights on levels of risk from residential radon. Also informative will be an analysis of pooled lung cancer data sets of women exposed to indoor radon in New Jersey, Sweden, and China.

A second survey of medical x-ray workers in China identified high risks of leukemia and cancers of the skin, breast and thyroid, but only among workers employed prior to the 1950's when radiation protection guidelines were less stringent. Blood from a sample of radiologists will be analyzed at the Lawrence Livermore National Laboratory for somatic mutations that may be related to cumulative radiation exposure.

Breast cancer was increased among young women with scoliosis who received frequent diagnostic x-rays of the spine. Pregnancy following exposure to the atomic bombings in Japan appeared to enhance the subsequent risk of radiation-induced breast cancer. Women over the age of 40 at the time of exposure to multiple chest fluoroscopies for tuberculosis were at a reduced risk of radiogenic breast cancer, as were older Japanese survivors of the atomic bombings. The presence of germline mutations of the p53 tumor suppressor gene will be determined among certain groups of women who developed radiogenic breast cancer at a young age.

Diagnostic x-rays were not causally related to adult leukemia or lymphoma in a study of members of prepaid health plans. However, there was some increasing risk for multiple myeloma with increasing number of x-rays. In a Swedish study, prenatal x-rays were associated with an increased risk of childhood cancer among twins. However, cohort studies of leukemia risk in twins born in Connecticut and Sweden did not reveal an excess, despite the greater exposure to prenatal x-rays of twins than single-born children.

High doses of iodine-131 to treat hyperthyroidism or thyroid cancer were not convincingly linked to increased risks of leukemia, indicating that the carcinogenic potential of this exposure is less than x-rays or gamma rays. Stomach cancer was the only malignancy for which there was a suggestion of dose-related risk. A study of patients given diagnostic doses of iodine-131 has been initiated, and includes head and neck examinations to ascertain thyroid nodular disease. In collaboration with the Laboratory of Human Carcinogenesis, the presence of mutations in p53 and K-ras genes in lung

cancer and adjacent healthy tissues is being evaluated in Thorotrast patients, atomic bomb survivors, NHL cases, and women exposed to high levels of indoor radon.

Low-dose radiotherapy to treat uterine bleeding induced more leukemias than higher doses given for cancers of the uterine corpus and breast, suggesting the importance of cell-killing in defining dose-response relationships. High-dose radiotherapy, however, was linked to an increased risk of thyroid cancer following treatment for childhood cancer. Radiotherapy also greatly increased the risk of death from osteosarcoma among children with bilateral (but not unilateral) retinoblastoma, consistent with interactions between genetic susceptibility and radiation exposure. Radiotherapy and chemotherapy for breast cancer appeared to interact in a multiplicative fashion to increase the risk of leukemia.

Tuberculosis patients, given multiple chest fluoroscopies during lung collapse treatments between 1930-1954, were recently re-surveyed in Massachusetts. Analyses of the data found that repeated, relatively low radiation doses imparted some risk of breast cancer, which appears cumulative, with linearity best describing the dose-response relationship. Basal cell carcinomas of the trunk were also found to be related to the number of fluoroscopies. Similarly, radiation treatments for ringworm of the scalp in Israel increased the risk of skin cancer of the head and neck.

Environmental Pollution: In Shenyang and Harbin in northeast China, cigarette smoking was a strong risk factor for lung cancer, with the higher prevalence of smoking among females, compared to elsewhere in China, contributing to the area's high rates. Indoor air pollution was also a significant factor, with risk rising in proportion to exposure to pollutants from coal-burning stoves and other home-heating devices. In addition, outdoor air pollution was linked to lung cancer risk, especially among residents exposed to inorganic arsenic emitted from stacks of a large copper smelter. This finding is consistent with earlier NCI studies pointing to arsenical air pollution as a cause of lung cancer in the United States. Studies are continuing to evaluate the role of chlorinated drinking water in the development of bladder and other cancers.

Nutrition: International correlations, studies of migrant populations, a variety of cohort and case-control studies, and experimental evidence indicate that dietary and nutritional factors play an important role in cancer etiology. Exploration of these factors continued, with an emphasis on biochemical measurements to clarify the influence of micronutrients and other dietary constituents.

A large case-control study of breast cancer among women of Asian ancestry in California and Hawaii found that the place of birth of the subject and her grandparents had a major impact on risk, as did the rural or urban nature of the place where the subject lived prior to migration. The age at migration did not affect risk unless migration occurred prior to age 15, suggesting that the childhood-adolescent years are crucial in determining risk or that relevant lifestyles (e.g., diet/nutrition) are not altered unless migration occurs early in life.

A case-control study of endometrial cancer in five U.S. areas found that obesity is a major predictor of risk. The timing and distribution of weight

gain and nutritional intake data are currently being examined in relation to risk. Information on fat storage, using blood samples and fat biopsies, will be used to supplement interview data, as will results of micronutrient and hormonal assays.

A case-control study of invasive and *in situ* cervical cancer in five U.S. communities found no association with the intake of carotenoids, vitamin A, or vitamin C. In a study of invasive cervical cancer in Latin America, however, higher risk was associated with lower dietary intake of vitamin C and β -carotene. An effect for low β -carotene is supported by serologic analyses among the early-stage cases. Data on blood nutrient levels are currently being evaluated in the U.S. study, which may explain the differences between the two studies. Neither study found an effect of low dietary or serum folate levels, as reported by some investigators.

A case-control study in Chicago and upstate New York found no evidence that vulvar cancer risk was affected by intake of vitamin A, total carotenoids, β -carotene, vitamin C, or folacin. However, clear increases in risk were observed with decreased intake of dark yellow-orange vegetables and α -carotene, which is concentrated in this vegetable subgroup. The dietary analysis was one of the first to employ data on the levels of individual carotenoids in common vegetables and fruits.

In a multicenter case-control study of oral cancer in the United States, dietary analyses among blacks found protective effects associated with fruit and vegetable consumption and dietary vitamin C and fiber, similar to earlier findings among whites.

In Linxian, China, two large-scale randomized intervention trials drew near completion. One trial focuses on 3,400 persons with esophageal dysplasia, while the other involves 30,000 villagers from the general high-risk population. Participants have been randomly assigned to one of several groups to receive different combinations of vitamins and minerals or placebo over a six-year period. A two-group design (multivitamins vs. placebo) is being used for the dysplasia trial. A more complicated eight-group design, based on a one-half replicate of a 2^4 factorial design, is used for the general population trial. The studies, now in their sixth and fifth years, respectively, will evaluate whether certain groups of vitamins and minerals can inhibit late-stage progression to cancer in a high-risk population with multiple micronutrient deficiencies.

Data analyses continued from a case-control study of stomach cancer in Italy, in collaboration with the Center for the Study and Prevention of Cancer in Florence and other institutions. For both intestinal and diffuse type stomach cancer, increased risks were associated with certain traditional soups and meats, while decreased risks were linked to intake of fresh fruits and vegetables, notably garlic, and vitamins C and E.

Medications: Studies continued to evaluate the carcinogenic effects of hormones, cytotoxic drugs, and other medicinal compounds. Analyses of cancer incidence in a large cohort of Swedish women treated with non-contraceptive estrogens revealed a significantly increased risk of endometrial cancer, a slightly decreased risk of cervical cancer, and no increase in risk of cancers of the ovary, pancreas, large bowel, or kidney. The risk of liver and biliary

tract cancers was significantly lower than expected, while the risk of breast cancer was slightly elevated. Breast cancer risk increased with duration of use, reaching 1.7 after nine years. Unlike the effect on endometrial cancer risk, the excess risk of breast cancer was not decreased by the addition of progestin to the regimen.

Based on ten years of follow-up of participants in the Breast Cancer Detection Demonstration Project, preliminary results indicate a reduced risk of all-cause mortality associated with ever-use of menopausal estrogens. The lower risk appears limited to recent users, with no further protection conferred by extended usage. Also, the decreased risk is mainly among women with low family incomes, suggesting that social class differences between estrogen users and non-users contribute to the effect.

Investigations continued of the health risks related to various methods of contraception. Users of barrier methods were found to be at a reduced risk of invasive cervical cancer, presumably because of concomitant use of spermicides with anti-viral activity, in a U.S. case-control study. In a study in Latin America, the use of injectable contraceptives was associated with an increased risk of cervical cancer. Because of reports linking the extended use of oral contraceptives to increased risk of breast cancer, a multicenter case-control study, focusing on premenopausal women, is underway in three U.S. regions. Both random digit dialing and area controls are being utilized, and oral contraceptives usage is being validated against medical records. The study is also collecting information on alcohol consumption and diet in adolescence and adulthood.

A population-based study of renal cell cancer was initiated to clarify findings from recent studies, including one by NCI, implicating diuretics as a major risk factor. Over 600 patients with renal cancer in Minnesota, which leads the nation in the incidence of this cancer, will be enrolled. In collaboration with the Gynecologic Oncology Group, the carcinogenicity of cisplatin and doxorubicin is being evaluated in survivors of ovarian cancer. Several other studies are evaluating the carcinogenic effects of various alkylating agents used in the treatment of childhood and adult cancers.

Genetic Susceptibility: Families at high-risk of developing cancer and heritable disorders predisposing to neoplasia are studied in an interdisciplinary approach to identify genetic mechanisms of cancer susceptibility.

After a two-decade search, a collaborative study with the Massachusetts General Hospital Cancer Center identified the p53 tumor suppressor gene as the site of the inherited defect in the Li-Fraumeni syndrome (LFS). This disorder features an autosomal dominant pattern of diverse cancers, particularly sarcomas of bone and soft tissue, breast cancer, acute leukemia, brain tumor, and adrenocortical carcinoma. In the five LFS families that were examined, all showed germline point mutations in the p53 gene. In one family, the mutation co-segregated with cancer in four relatives. In tumor specimens of family members, the wild-type p53 allele was deleted in the cancer cells, as expected in recessive tumor suppressor genes. These findings should lead to new means for prevention, early detection and perhaps treatment, as well as a broader understanding of carcinogenesis.

Familial melanoma and the dysplastic nevus syndrome (DNS) continued to receive attention. An updated analysis revealed relative risks of 500 for subsequent melanoma in those family members with a prior melanoma. Melanoma risks for those members with DNS, but not melanoma, was 100-fold higher than the general population, and the actuarial estimate of cumulative lifetime risk of melanoma in DNS patients approached 100 percent. A case-control study of dysplastic nevi found that most affected patients also had first degree relatives with dysplastic nevi. Efforts continued to verify and further delineate the gene responsible for the DNS-melanoma syndrome. One session of this year's Genetic Analysis Workshop addressed the initial localization, by staff members, of the gene to chromosome 1p. Eight new families are being studied to determine if this finding can be replicated.

Follow-up studies have continued of a family with 10 cases of renal cancer and a translocation between chromosomes 3 and 8. Studies have shown chromosome 3p rearrangements or deletions in nearly all renal cancer tissues of non-familial cases, suggesting its importance to the development of this neoplasm. In the past year, all five surviving cases of renal carcinoma in the t(3;8) family developed recurrent disease. Chromosome and molecular genetics analyses of fresh tumor tissue unexpectedly showed that the derivative 8 chromosome, with the rearranged distal 3p, had been deleted. Work is in progress to identify the critical gene(s) involved in the origins of hereditary renal cancer.

Studies continued of patients with neurofibromatosis 2 (NF2), whose major manifestation is bilateral acoustic neuromas that lead to deafness and loss of balance. Posterior capsular lens opacities were found in 21/26 (81%) of the patients who were from multigeneration NF2 families and in 13/14 NF2 sporadic patients. This year, two other ocular abnormalities were identified: cortical wedge opacities in nine patients and a retinal gliosis in four patients from one family. Gene mapping studies suggest that the NF2 gene is on chromosome 22, though further work is needed to confirm this linkage assignment. Family studies continued of multiple endocrine neoplasia syndrome type I, multiple basal cell carcinoma syndrome, Hodgkin's disease, chronic lymphatic leukemia, and cancers of the bladder and ovary.

Metabolic differences as markers of cancer risks continued to be investigated for lung and bladder cancers in collaboration with the Laboratory of Human Carcinogenesis. The ability to metabolize the drug debrisoquine, a measure of the function of one P-450 isozyme, was related to lung cancer risk in a case-control study. Compared to poor metabolizers, intermediate metabolizers had a fourfold excess risk of lung cancer, while a 16-fold excess risk was observed in extensive metabolizers.

Infectious Agents: Epidemiologic data suggest that cervical neoplasia is related to a sexually-transmitted infectious agent. Recent laboratory and epidemiologic studies have identified human papillomaviruses (HPV) as most likely involved in this disease. Ongoing epidemiologic studies have focused on: 1) defining the prevalence of HPV infection among normal women in order to provide control estimates for interpreting HPV positivity among women with cervical neoplasia, 2) investigating risk factors for HPV infection on the assumption that it should share many of the risk factors as cervical neoplasia, and 3) undertaking prospective investigations to evaluate whether HPV-infected women are more likely than uninfected women to develop new or progressive cervical neoplasia. Over the past year, these studies have

yielded results supporting the causal role of HPV infection in cervical neoplasia.

A prevalent case-control study of women with cervical intraepithelial neoplasia (CIN) revealed that over 80 percent of the cases had detectable HPV, compared with 18 percent of controls. Although the number of genital HPV types exceed 20, only a few (notably types 16, 18, 31, 33, and 51) were found in the great majority of women with high-grade CIN, confirming earlier reports. In a correlational study of students, HPV infection was associated with other cervical neoplasia risk factors, including lifetime number of sexual partners, oral contraceptive use, and black race (independent of the measured behavioral factors). Another survey found that HPV prevalence was inversely correlated with socioeconomic status.

The first prospective data, though still too scanty to be definitive, suggest that HPV infection precedes and predicts the appearance of cervical neoplasia. Eleven (52%) of the first 21 cases of incident dysplasia in a large cohort study had detectable HPV in cervical smears taken a year before diagnosis, when they were judged to be cytologically normal, compared to 63 control women (16%). Thus, the presence of HPV appears to indicate either abnormal cytology missed by screening or an increased risk of developing new disease.

Based on descriptive epidemiologic data, adult T-cell leukemia (ATL) is etiologically linked to HTLV-I exposure in early life. Recently, the infective dermatitis syndrome of childhood was linked to HTLV-I infection in Jamaicans, suggesting a precursor syndrome related to the immunodeficiency induced by the virus. In collaboration with laboratory investigators, molecular analysis of ATL cases demonstrated an overexpression of the immune modulating transforming growth factor beta ($TGF-\beta$), supporting the concept that viral-related immunosuppression plays an etiologic role in ATL. The finding of elevated spontaneous lymphocyte proliferation in seropositive subjects may represent an intermediate pathway by which HTLV-I amplifies its target cells.

A recent preliminary finding that farming is associated with increased lymphoma risk in Jamaica suggests the influence of exposures to agricultural chemicals, perhaps involving immune modulating effects. Lymphoma risk may also be increased by antigenic stimulation from myriad parasitic infections in areas of extreme poverty.

Infection by HTLV-II is emerging as a major problem among drug abusers, including addicts from the early 1970's. Spontaneous lymphocyte proliferation occurs among HTLV-II infected subjects, though at a lower level than among persons infected with HTLV-I. Reservoirs of HTLV-II have been identified among American Indian populations in the southeastern and western United States, Brazil, and Panama. In one hospital survey of intravenous drug abusers, no specific disease was found associated with HTLV-II infection.

Efforts continued to estimate the magnitude of the human immunodeficiency virus (HIV) epidemic and project its impact on cancer, particularly non-Hodgkin's lymphoma (NHL), in the United States. Using backcalculation modeling, some 700,000 persons were infected with HIV by 1985, and perhaps one million by 1987. In homosexual and hemophilia cohorts established by the

Program, an increased risk of developing NHL was observed, which markedly accelerated eight years after seroconversion.

It is now projected that over 4,000 excess cases of NHL (i.e., in excess of expected numbers from the pre-AIDS era) will occur in 1994, constituting approximately 10 percent of all NHL. Except for Kaposi's sarcoma, no clear excesses of other cancers related to HIV infection have been uncovered. In other studies, however, HIV-related immune deficiency has been associated with anal epithelial atypia in relation to HPV activation and with sexual transmission of hepatitis C virus, which has been linked recently to hepatocellular carcinoma.

Biostatistics: Research continued on developing statistical methods, many of which have been incorporated into a comprehensive computer program, for use in epidemiology. Completed work includes the efficient point and interval estimation of attributable risk in stratified case-control studies, tests of validity for pooling, and bias induced by improper pooling. Other research includes sample size determination, taking cost into account; analyses of certain play-the-winner clinical trials; methods for analyzing sparse data, such as arises in the distribution of mutations in a gene of known sequence; analysis of survival curves produced by *in vitro* exposure of cultured cells to DNA-damaging agents; and statistical methods for evaluating Gm immunoglobulin data.

General methods of logistic analysis were developed for case-control studies in which controls are obtained by cluster sampling. A comprehensive review of methods of selecting controls for case-control studies is nearing completion. Papers were published on efficient statistical methods for studying large cohorts. Comparisons were made of the statistical efficiency of case-cohort, nested case-control and other designs, while work continued on Poisson regression analysis for case-cohort data.

Methods were also reviewed for incorporating validation data to correct errors in measurements of exposure in the analysis of case-control studies, and new methods of analysis were developed. The efficiency of various methods of analysis depends on whether exposure measurement errors are differential or non-differential. Related work shows how preliminary validation studies can be used to determine the value of subsequent data on disease status and error-prone exposure measurements. Another series of studies concerned collapsing polychotomous exposure measurements into coarser categories. Even if measurement errors were non-differential originally, the coarser exposure categories may exhibit differential misclassification, with bias away from the null or even a reversal in the direction of observed exposure effects. Similar results hold for clinical trials in which a combined clinical endpoint is composed of several component conditions. Even though blinded assessment assures non-differential misclassification of the component conditions, the assessment of the combined endpoint may be seriously distorted.

Analyses were completed on the assessment of absolute risk of disease in cohort studies and on inference for attributable risk based on logistic regression of case-control data. Work is in progress to evaluate the uncertainty of estimates of absolute risks derived from population-based case-control studies. As an example, these results will yield ranges of

uncertainty together with estimates of risk of developing breast cancer over a given time period for a woman with specified risk factors.

COLLABORATIVE ACTIVITIES

Interagency Programs: Collaborative studies with other Federal agencies continued to receive high priority to: (1) evaluate urgent issues to which epidemiology can make a contribution, including those of immediate regulatory or public policy concern; and (2) stimulate the epidemiologic use of technical and data resources developed by the government for other purposes. Although many research and regulatory agencies are concerned with environmental causes of cancer, few have epidemiologic expertise. During this time of fiscal restraint, it is important to increase initiatives to develop and coordinate national data resources that, with proper safeguards, may be utilized for epidemiologic research.

The National Death Index (NDI) of the National Center for Health Statistics (NCHS) continued to serve the needs of investigators in the Program. An effort to extend the NDI further back in time (i.e., before its initial year in 1979) was terminated due to budgetary constraints. The technical feasibility of such an extension was demonstrated, however, with many states participating in the effort.

Efforts to develop a national database for occupational mortality centers on the Continuous Work History Sample (CWHHS). The CWHHS is a one-percent sample of Social Security Administration (SSA) numbers begun in 1957, and is limited to the industry of the employer. Its small size (i.e., 2.6 million) is somewhat offset by its longitudinal character. Technical difficulties that have delayed full testing of the CWHHS appear to be near resolution. Its utility will be determined by its capacity to reveal well-known mortality differentials during the period 1973-1977.

The Internal Revenue Service (IRS) collaborated with the Program to develop coding procedures of taxpayers' occupations. These procedures were applied to the 1979 Statistics of Income (SOI) sample of taxpayers, permitting a test of the usefulness of adding IRS occupational information to industry information from SSA. If the test is successful, consideration could be given to adding the occupational information to the CWHHS. Death certificate data on cause of death were obtained for the 1979 SOI sample, and the IRS is preparing the file for analysis by Program investigators.

In a joint effort with the NCHS and NIOSH, the Program assisted in developing a database for occupational mortality in several states. The data include death certificate information on usual industry of employment and occupation of decedents. With the assistance of the Bureau of the Census, standard codes and coding practices were established, and coders trained. By the end of 1990, the file grew to about 3.5 million death records.

Accession of address information is important to Program epidemiologists in locating potential study subjects. The IRS address file has been a resource for investigators working on occupational health problems or studies of war veterans. Currently, a legislative initiative is being revived that would expand access to the file, allowing its use by investigators involved in other types of medical follow-up studies.

A database of 14 million hospital visits (5 million patients) to the more than 100 U.S. Veteran Administration (VA) hospitals has been used to select cohorts and examine cancer risk compared to internal (VA) and external (Surveillance, Epidemiology and End Results) [SEER] rates. The data have provided information on the relation between prostate cancer and transurethral prostatectomy. Computer analyses of rheumatoid arthritis, infectious mononucleosis, acromegaly, splenectomy, and vasectomy cohorts are being expanded to include additional years of data.

Close collaboration between Program staff and NIOSH continued for a number of epidemiologic and methodologic issues of mutual interest. Collaborative investigations underway include mortality studies of workers exposed to acrylonitrile, silica and other dusts, and embalming chemicals. A project to identify biologic markers for bladder cancer has recently been initiated among workers exposed to aromatic dyes. Feasibility efforts are assessing epidemiologic opportunities to evaluate suitable populations occupationally exposed to 2,4-D, alachlor, phenylphenol, inorganic acid mists, formaldehyde-based resins, propylene oxide, perchloroethylene, Stoddard solvent, and diesel exhausts.

International Projects: Program staff members continued to be involved in activities related to the health effects of Soviet citizens exposed to ionizing radiation from the Chernobyl nuclear reactor accident. During the fall, visits to Minsk and Kiev were made by an NCI-convened group to encourage formal studies of leukemia and to plan for a workshop on the subject. A second visit was made to Kiev in December, 1990, for a workshop on the detection of thyroid dysfunction. The workshop was preceded by a symposium on thyroid disorders in Chernigov, sponsored by the World Health Organization (WHO). Steps were taken toward formulating a protocol for a collaborative study of thyroid disease, including neoplasia. Political unrest and changing personnel at the All-Union Scientific Center of Radiation Medicine in Kiev complicated collaborative efforts, such as visits by Soviets to the United States for planning and training related to the design of studies. Other international activities include a ten-year WHO Program (with \$20 million provided by a Japanese donor) and survey studies by the International Atomic Energy Agency. A third visit in the spring 1991 will finalize the agenda for a workshop in the United States. U.S.-Japan workshops were held 1) on transgenerational carcinogenesis (observed in animal studies and suggested in Sellafield, England, where preconceptional radiation exposures of nuclear reactor workers were related to risk of leukemia in their offspring); and 2) on kidney tumors, including research of Program staff on Wilms' tumors in relation to congenital aniridia, hemihypertrophy, Beckwith-Wiedemann syndrome, and familial occurrences.

Other Activities: Efforts continued to encourage interaction between the epidemiology and biostatistics components within the Program, to stimulate interdisciplinary studies with laboratory scientists in other parts of the Division and elsewhere, and to transfer etiologic findings to prevention-oriented programs. Program staff members continued to coordinate case-control and other analytical studies with extramural investigators at cancer centers, prepaid health plans, SEER cancer registries, and elsewhere. Comprehensive and critical reviews on a wide variety of topics were also prepared by members of the Program.

Program scientists served as members on a wide-range of committees, working groups, and similar bodies concerned with public health and policy issues. These include an advisory panel to the NCHS Director on the operation of the NDI; a committee of the Office of Science Technology and Policy (OSTP) concerned with radiation research and policy coordination; a Public Health Service working group on the benefits and potential risks of fluorides; a Commission of European Communities examining the feasibility of studying populations exposed to fallout from the Chernobyl nuclear accident; working groups of the International Agency for Research on Cancer to review risks associated with various chemical exposures; a committee on Interagency Radiation and Policy Coordination to prepare a statement on risk estimates based on the 1990 BEIR V Report; committees of the National Council on Radiation Protection and Measurements dealing with indoor radon, hazards of space radiation to astronauts, and prenatal effects of ionizing radiation; advisory committees of the National Academy of Sciences concerning issues of indoor radon, biological effects of ionizing radiation (BEIR V), and effects of nuclear weapons tests in the Pacific. Program staff members also contributed to departmental and interagency committees related to the health effects of AIDS, asbestos, formaldehyde, pesticides, water pollution, passive smoking, smokeless tobacco, ultraviolet radiation and ozone layer depletion, and Kuwaiti oil fires and spills, as well as the use of epidemiology in risk assessment and management.

EXTRAMURAL PROGRAMS

The Extramural Programs Branch plans, develops, directs and manages extramural research in biometry, epidemiology, genetic epidemiology, and related multidisciplinary activities. These activities include evaluating program effectiveness, providing scientific and administrative information, advising on extramural funding needs, developing new initiatives, managing research resources, and meeting with investigators to exchange scientific information and keep abreast of research trends.

The Biometry program supports the development of statistical methods for the design, conduct and analysis of epidemiologic/biomedical studies with the goal of delineating mechanisms of cancer etiology. A workshop will be held in the summer of 1991 to discuss how recent developments in theoretical biostatistics and computing can be incorporated into the analytical resources (e.g., statistical packages) that are available to epidemiologists.

The Epidemiology program supports research into the origins and natural history of neoplasia in humans, demographic and geographic variation in the occurrence of cancer, identification of cancer risk factors, development of information basic to cancer prevention, and creation of new methods to improve the precision and accuracy of epidemiologic and multidisciplinary studies. This year, the proceedings of a 1990 workshop on the epidemiology and biology of multiple myeloma, held in collaboration with the NCI Organ Systems Program, were edited by staff members and will soon appear as a monograph. A Request for Applications (RFA) was issued as a result of a Branch workshop on unusual risks of certain cancers among ethnic/minority groups. Over 50 grant applications were received, and it is anticipated that five to eight new projects in this high-priority research area will be funded. Since cancer rates in the aged have not shown much improvement for many cancer sites, the Branch plans to organize a workshop to focus attention on the rise in cancer

incidence with advancing age, and to generate ideas for etiologic and prevention research.

The Genetic Epidemiology program supports projects on interactions between genetic susceptibility and environmental exposures in the etiology of cancer. Research focuses on the analysis of the genetic component to various tumors, and on the study of risk factors in familial clusters of cancer, using epidemiologic and multidisciplinary approaches. A conference on methodological developments and analytic needs in genetic epidemiology is being planned for the winter of 1991-92.

The Biochemical/Molecular Epidemiology program encourages the development and application of laboratory methods for epidemiologic studies of cancer etiology. Efforts are focused on the identification and validation of biomarkers of host susceptibility and/or exposure to carcinogenic agents. In conjunction with a conference organized by the International Agency for Research on Cancer, a workshop will be held in the fall of 1991 to define epidemiologic directions in this research area.

The Retroviral and HIV-Related Epidemiology program supports and coordinates studies to define the incidence, natural history, and risk factors for malignancies and premalignant conditions associated with retroviral infections, including the human immunodeficiency virus (HIV). Of particular interest are studies on the effect of viral strain variation, co-infections with multiple viruses, genetic factors, immune alterations, anti-viral treatments and environmental exposures on the development and progression of virus-associated neoplasia. During the year, a meeting was held of grantees working in AIDS-related research, which resulted in the interchange of data from work-in-progress and sharing of research resources and questionnaires. Further emphasis will be given to HIV-associated cancer risks in women and children, and efforts will continue to understand the pathogenesis of Kaposi's sarcoma, lymphomas, and other tumors reported in HIV-infected individuals.

The Viral Epidemiology program emphasizes the epidemiologic study of risk factors and mechanisms associated with human papillomaviruses (HPV) and hepatitis B virus (HBV).

The Small Business Innovation Research (SBIR) program is now encouraging submission of grant applications rather than support through the contract mechanism for this congressionally-mandated initiative. From 1985 to the present, 19 contract solicitations resulted in 28 phase I awards and 7 phase II awards. During FY-91, 21 SBIR grant applications were received, and three phase I and three phase II grants were funded.

PROSPECTS

The Program will continue to pursue a comprehensive, flexible, and balanced approach to generate new ideas and answer important questions in cancer epidemiology and biostatistics. Emphasis will be given to in-depth analytical studies to identify etiologic agents and elucidate mechanisms of carcinogenesis. Efforts will continue to utilize data resources of the NCI and other Federal agencies for epidemiologic investigations. Future directions will be defined by new research findings, resource opportunities, and laboratory advances that can be utilized for epidemiologic purposes.

This period is particularly exciting as epidemiologic and experimental approaches are merging, and clues to understanding cancer are unfolding at a rapid rate. Epidemiologic investigations of environmental and lifestyle risk factors, such as nutrition, will increasingly incorporate biochemical and molecular components into their study designs. These laboratory measures will provide important information on exposure levels, biological response, preneoplastic lesions, susceptibility states, and mechanisms of action. Studies of cancer-prone families and genetic syndromes provide exceptional opportunities to apply new molecular techniques, such as those related to the role of tumor suppression genes and oncogenes. Emphasis will continue to be given to genetic epidemiology in an effort to keep pace with the dramatic progress being made in molecular genetics.

Descriptive studies will continue to be important in generating etiologic clues to cancer. Data from the SEER program, NCHS, and other sources of cancer statistics will be analyzed to define time trends, geographic clustering, ethnic/racial variations, and other demographic characteristics of cancer. Program emphasis, however, will be placed on analytical studies to identify a wide variety of environmental and host factors, and their interactions, in the development of cancer. Further emphasis will be placed on clarifying the role of infectious agents, with special attention to the epidemic of AIDS-associated neoplasia.

Emphasis will be given to identifying reasons for excess rates of certain cancers among racial and ethnic groups and to gender-specific cancer sites (e.g., breast, prostate, ovary, and uterus), as well as to the role of endogenous and exogenous hormones on cancer risk. Attention will also be given to those tumors with a disproportionate burden among the elderly, as well as those showing increasing rates over time (e.g., NHL, melanoma, multiple myeloma, and adenocarcinomas of the esophagus and gastric cardia). While emphasis will be given to studies of major tumors, investigations of relatively uncommon neoplasms will continue to be important in further understanding the origins and basic mechanisms of cancer.

Biostatistical approaches will continue to be evaluated and developed, particularly as they relate to investigations of carcinogenic mechanisms and cancer biology, to research into quantitative risk assessment, and to interdisciplinary studies involving epidemiologic and laboratory collaborations. Epidemiologic and biostatistical support will continue to be provided to a wide variety of groups within the NCI and elsewhere.

Interaction and coordination of epidemiologic and biostatistical elements of the National Cancer Program will remain important goals of the Program. Efforts will continue to increase and broaden the scope of extramural and cooperative research activities. In particular, Request for Applications (RFAs) will be developed based on workshops and other forums held to identify seminal issues in cancer etiology. Emphasis will continue on collaborative activities that draw upon the expertise and resources of the extramural community and other governmental agencies. Advantage will be taken of binational agreements and other international programs offering unique opportunities to investigate the etiology and prevention of cancer in humans. Finally, the Program retains a strong commitment to the training of young investigators interested in careers in cancer epidemiology, biostatistics, and related areas.

ANNUAL REPORT OF
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EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1990 through September 30, 1991

The major functions of the Biostatistics Branch are to conduct independent and collaborative investigations, using biometric approaches, into the distribution and determinants of cancer in individuals and populations; to develop and evaluate statistical methods for the design, conduct, and analysis of epidemiologic, experimental and clinical studies of cancer; to conduct basic research in mathematical statistics related to various aspects of cancer; to explore mathematical models to clarify processes of cancer biology and carcinogenesis; to provide statistical consultation to NCI intramural scientists and other groups concerned with cancer research; and to plan and conduct research and developmental work to improve methodology in the application of computers and data processing techniques for cancer research and related programs.

The work of the Biostatistics Branch is accomplished through in-house studies and collaborative projects involving other investigators in this country and abroad. Following is a brief summary of the program of research during the year. Activities are listed according to section, although often members of several sections are involved in individual projects.

Mathematical Statistics and Applied Mathematics

Activities of the Mathematical Statistics and Applied Mathematics Section are principally concerned with research in statistical methods useful in cancer research and collaboration in the conduct of cancer studies with other branches and laboratories, both within and outside the Division of Cancer Etiology (DCE).

Research continued on statistical methods useful in epidemiology. Completed work includes the efficient point and interval estimation of the attributable risk in stratified case-control studies, as well as tests of the validity of pooling and the bias induced by improper pooling. Other research includes sample size determination taking cost into account. Most of these methods have been incorporated into a comprehensive computer program.

Other statistical research includes the proper analyses of certain play-the-winner clinical trials, methods for analyzing sparse data, such as arises in the distribution of mutations in a gene of known sequence, the analysis of survival curves produced by in vitro exposure of cultured cells to DNA-damaging agents and statistical methods for Gm immunoglobulin data.

Collaboration continued with investigators both within and outside of DCE, including work with Epidemiology and Biostatistics Program staff on testicular cancer, multiple myeloma, and lymphoma (described elsewhere). Research with other programs in DCE includes statistical analyses for studies of DNA repair

defects in Cockayne's syndrome and xeroderma pigmentosum, the effect of carbon dioxide pressure on canine coronary sinus flow, the susceptibility of radiation-induced chromatid damage, cisplatin treatment and platinum-DNA adducts, and the distribution of point mutations in the p53 tumor suppressor gene.

Collaboration with other divisions included a study evaluating antigen positive tumor cells and test hybridoma cells from patients with cancer-prone diseases and experiments performed to identify genes inducible by ionizing radiation.

Epidemiologic Methods

The Epidemiologic Methods Section conducts research to develop, adapt, and evaluate methodologic procedures useful in epidemiologic studies of cancer. Emphasis is placed on statistical and operational methods for the design, implementation, interpretation and analysis of a broad range of human studies, including both observational and experimental designs.

Work was published on the cost-efficient allocation of controls to strata when costs of obtaining controls vary among strata, and sample size calculations appropriate to such designs are in development. General methods of logistic analysis have been developed for case-control studies in which controls are obtained by cluster sampling. A comprehensive review paper on methods of selecting controls for case-control studies is nearing completion.

Papers were published on efficient statistical methods for studying large cohorts. One paper compared the statistical efficiency of case-cohort, nested case-control and other designs, and another report discussed practical and theoretical advantages of various designs. Work continues on Poisson regression analysis for case-cohort data.

Methods were reviewed for incorporating validation data to correct errors in measurements of exposure in the analysis of case-control studies, and new methods of analysis were developed. The efficiency of various proposed methods of analysis depends on whether exposure measurement errors are differential or non-differential. Related work shows how preliminary validation studies can be used to determine the value of subsequent data on disease status and error-prone exposure measurements. Another series of studies concerned collapsing polychotomous exposure measurements into coarser categories. Even if measurement errors were non-differential originally, the coarser exposure categories may exhibit differential misclassification, with bias away from the null or even a reversal in the direction of observed exposure effect. Similar results hold for clinical trials in which a combined clinical endpoint is composed of several component clinical conditions. Even though blinded assessment assures non-differential misclassification of the component conditions, the assessment of the combined endpoint may be seriously distorted.

Papers were published on the assessment of absolute risk of disease in cohort studies and on inference for attributable risk based on logistic regression of case-control data. Work is in progress to assess the uncertainty of estimated absolute risks derived from population-based case-control studies. These results will be applied, for example, to providing ranges of uncertainty together with estimates of the risk of developing breast cancer over a given time period for a woman with specified risk factors.

Backcalculation models have been developed to project AIDS incidence in the 1990s while taking into account the effects of therapy and changes in the surveillance definition of AIDS. These models project a plateau of AIDS incidence at high levels for the next five years. Models were also developed to project the incidence of AIDS-related non-Hodgkin's lymphoma (NHL). These models indicate that between 8% and 27% of all NHL reported in 1992 will be attributable to HIV infection. Previous work was published assessing the reliability of estimates of seroprevalence obtained by backcalculation and describing flexible regression methods for backcalculation.

Other AIDS-related work includes developing smooth estimates of the hazard function appropriate for left and right censored cohort data and developing methods to estimate the probability of perinatal transmission of HIV.

Analytical Studies

The Analytical Studies Section conducts investigations to generate and evaluate hypotheses regarding the causes of cancer in human populations. Staff members often work collaboratively with other scientific groups in the United States and abroad to gather and analyze epidemiologic data to assess environmental and host determinants of cancer.

Analyses of cancer incidence and mortality: Evaluations of the variation in cancer rates over space and time can often provide leads to etiologic factors. During the year, it was shown that colon cancer incidence now is higher among males than females, and among blacks than whites; increasing incidence is partially due to earlier stage at diagnosis. Major analyses of incidence and mortality rates in relation to fluoridation of the water supply revealed no causal association. Childhood leukemia patterns were evaluated using data from 28 registries; important differences were identified among ethnic groups, including the identification of very low rates in blacks and high rates in some Hispanic populations. Comparison of cancer incidence, survival, and mortality rates among racial/ethnic minority groups continued in attempts to delineate high-risk groups. Analyses of the descriptive epidemiology of many adult cancers are continuing, utilizing histologic information to better characterize distinct tumor subgroups of etiologic significance. Following the observation of declining lung cancer rates among the young, analysis by histologic cell type showed the decline to be most notable for squamous cell carcinomas; marked variations in incidence by race and sex were also noted for the various histologic groups. Published this year was a paper describing rising incidence of adenocarcinomas of the esophagus and gastric cardia, occurring predominantly among white men; these patterns contrast with the more generally known excess of squamous cell esophageal carcinomas among blacks and declines in stomach cancer. Age and cohort analyses of skin melanoma mortality rates during 1950-84 among whites in the United States indicate that males born during the 1920s and females born during the 1930s were at highest risk, and that future trends in annual age-adjusted rates may be expected to bend downward early in the 21st century.

Case-control and cohort studies in the United States: The Section undertakes collaborative analytical investigations to identify and quantify risk factors for various cancers. This year analyses of data from the largest investigation of oral and pharyngeal cancer, a case-control study involving nearly 1,200 cancer patients in Atlanta, New Jersey, Los Angeles, and the San Francisco area revealed

significant protective effects associated with vitamin supplement use, particularly vitamins E and A. Additional analyses found that users of mouthwash experienced an increased risk of oral cancer. The excess was only for mouthwashes high in alcohol content, suggesting that topical exposure to alcohol may increase risk of this cancer. Follow-up of the oral cancer patients continued during the year in attempts to ascertain the risks of second primary cancers and their causes.

Data are being analyzed from case-control studies of biliary tract cancer and renal pelvis and ureter cancers conducted in collaboration with the University of Southern California, the New Jersey Department of Health and the University of Iowa. Cigarette smoking has been found to account for almost 3 out of 4 of the cancers of the renal pelvis and ureter. Examination of the role of analgesics in the etiology of these tumors is also a prime focus. Cigarette smoking has been linked to biliary tract cancers in a preliminary analysis.

A large-scale, population-based study of renal cell cancer was initiated last year to pursue leads identified in recent studies, including one by NCI, implicating diuretics as a major risk factor. Over 600 patients with renal cancer in Minnesota, which leads the nation in incidence of this cancer, are being enrolled. Results from the study should be available before the end of 1992.

Based on data collected during the National Bladder Cancer Study, an analysis of the attributable risks for cigarette smoking, occupation, urinary tract infections, coffee drinking, artificial sweeteners, and tap water consumption in men and women is in progress. These factors, however, do not explain the male excess of bladder cancer, and biochemical studies have been initiated to identify sex-related determinants of risk.

A collaborative case-control study of 600 childhood acute lymphocytic leukemia cases and matched controls was organized with the Children's Cancer Study Group to evaluate the relationship of this neoplasm with exposure to residential magnetic fields, electrical appliances, and radon. A pilot study was completed this year that showed that certain spot and 24-hour measurements of magnetic fields within residences were highly correlated with direct exposures measured with personal dosimeters worn by children. The field data collection using this subset of measurements has recently begun.

Epidemiologic research is needed to determine whether diesel exhaust exposure increases lung cancer risk, and if so, to quantify the risk. To this end, NCI and the National Institute for Occupational Safety and Health (NIOSH) have initiated a pilot study to determine the feasibility of conducting a nested case-control study of lung cancer among miners, an occupational group with heavy exposure to diesel exhaust.

Analysis continued this year of data from of the 26-year follow-up of 250,000 United States veterans (Dorn Study). Dose-response relationships for cigarette smoking have been reported from myeloid leukemia, stomach, prostate, renal, and liver cancers. Similarly, in a 20-year follow-up of 17,633 men from the upper midwest and northeast regions of the United States, dose-response relationships for cigarette smoking have been identified for prostate cancer and lymphatic and unspecified leukemias. Dietary factors are being assessed for cancers of the lung, colon and rectum, and stomach.

In a multi-center case-control study of esophageal and pancreatic cancer, interviews with 1,000 patients and 2,150 population controls are being evaluated to determine whether dietary factors, cigarette smoking, alcohol drinking, medical conditions or other factors explain the excess of these cancers among blacks.

Also being analyzed are data from the 1986 National Mortality Followback Survey (NMFS), which involved the administration of a mail questionnaire to the next of kin of 20,000 decedents or about 1% of the deaths in the United States in 1986. Cigarette smoking and alcohol consumption have been identified as risk factors for nasopharyngeal cancer among whites in the United States with NMFS data. Recent analysis suggests that use of birth control pills is linked with liver cancer in women under age 50. Risk factors for small intestinal cancer, other endocrine tumors, and male breast cancer are presently being evaluated. Methodologic papers from the NMFS based on issues of mail questionnaire design and response rates have also been published this year.

Analysis of data from a collaborative case-control study, with the University of Iowa and University of Minnesota, of leukemias and non-Hodgkin's lymphoma among males confirmed some familial cancer associations previously reported and identified new ones with specific leukemia and lymphoma subtypes.

International studies: A major emphasis is the conduct of analytical biometric/epidemiologic studies in areas of the world that offer special opportunities for research on cancer etiology. The Branch is collaborating with institutions in case-control, cohort, and intervention studies in China, Japan, Italy, Sweden, Denmark, West Germany and Australia.

In Linxian, China, two large-scale randomized intervention trials drew near completion during the year. One trial focuses on 3,400 persons with esophageal dysplasia. The other involves 30,000 villagers from the general high-risk population. Participants have been randomly assigned to one of several groups to receive different combinations of vitamins and minerals or placebo over a 6-year period. A two-group design (multivitamin vs. placebo) is being used for the dysplasia trial. A more complicated eight-group design, based on a one-half replicate of a 2^4 factorial design, is used for the general population trial. The studies, now in their sixth and fifth years, respectively, will evaluate whether certain groups of vitamins and minerals can inhibit late-stage progression to cancer in a high-risk population with multiple micronutrient deficiencies.

In Shenyang and Harbin in northeast China, cigarette smoking was a strong risk factor for lung cancer, with a higher prevalence of smoking among females, compared to elsewhere in China, contributing to the area's high rates. Air pollution was also a significant factor, with risk rising in proportion to exposure to indoor pollutants from coal-burning Kang and other home-heating devices. No link to home radon was found, despite the use of year-long alpha-track radon detectors (the best monitors currently available) and the stability and large size of the population studied.

In an area of Shandong Province, China, with exceptionally high stomach cancer rates, precancerous gastric lesions (i.e., chronic atrophic gastritis, dysplasia) are being evaluated. Three thousand adults in this high-risk area were enrolled in a screening program to detect early cancers and to compare questionnaire items

and biochemical markers between groups with various precursor lesions. Initial results suggest that atrophic gastritis is nearly universal among adults, but dysplasia affects males about twice as often as females.

Three occupational cohort studies in China drew near completion during the year. Follow-up of approximately 100,000 workers exposed to benzene should enable the most precise estimation yet available of the benzene-leukemia dose-response relation, plus an evaluation of whether benzene induces other cancers. In a follow-up of 16,000 persons with silicosis in five provinces in central China, plus 54,000 persons heavily exposed to silica without silicosis, initial analyses suggest a relationship between silica exposure and lung cancer, although some inconsistencies exist. Follow-up of nearly 30,000 tin miners and smelter workers in Yunnan province, where lung cancer rates are exceptionally high, is assessing interactions between these carcinogens and examining time-related factors in cancer induction.

In Italy, analyses of data continued from a case-control study of stomach cancer, in collaboration with the Center for the Study and Prevention of Cancer in Florence and with other institutions. This year, for both intestinal and diffuse type stomach cancer, increased risks were associated with certain traditional soups and meats, while decreased risks were linked to intake of fresh fruits and vegetables, including garlic consumption. Analyses underway are seeking to detect the presence of oncogenes in tissue from patients with familial history of stomach cancer, and to evaluate correlations in risk with infection with *H. pylori*.

Collaboration continued with investigators in Sweden on the analysis of linked census, hospitalization and cancer registry data to evaluate occupational and other factors in the occurrence of several neoplasms. In addition, a multicenter study of renal cancer was launched in Sweden, West Germany, Denmark and Australia to evaluate diuretic and other drug use as well as a variety of environmental and host factors for this cancer which occurs at high rates in these areas. Data linkage of an in-patient register of the Uppsala health care region with the Swedish National Cancer Registry was used to evaluate risks of cancer following selected surgical procedures or medical conditions. Risks of cancers of the stomach, esophagus and pancreas were elevated following the diagnosis of pernicious anemia, and risk of primary liver cancer was elevated following the diagnosis of liver cirrhosis.

In Taiwan, where incidence of cervical cancer is one of the highest in the world, a prospective study of 7,000 women randomly selected from two townships was carried out to determine the role of human papillomavirus (HPV) infection and its persistence in the etiology of cervical neoplasia. In addition, the relationships of behavioral factors, such as sexual practices, reproductive history, use of oral contraceptives, smoking, and personal hygiene, with HPV infection and with cervical neoplasia will be evaluated in a nested case-control study.

Collaboration also continued with investigators at the Radiation Effects Research Foundation in Hiroshima, Japan, on the analysis of dietary factors, especially the role of western diet containing a high-fat content, in the etiology of colorectal cancer. In analyses of stored blood collected in 1970-72 from A-bomb survivors who later developed stomach cancer, significantly low levels of serum ferritin were detected. Low ferritin combined with the presence of achlorhydria

represented a strong predictor of stomach cancer risk, even when detected 10-20 years prior to cancer occurrence.

Information Resources Management

The Information Resources Management Section is responsible for assuring delivery of computer-related support to epidemiologists, biometricians, and other staff members throughout the Epidemiology and Biostatistics Program. The major recurring activities of the section include contract procurement and administration, information management and dissemination, and technical and consultative support to investigators in the conduct of research. This year, major activities included: 1) extending efforts to contain the costs for DCRT computing services; 2) planning for extended Local Area Network coverage; and 3) preparing for receipt of the 1990 census data.

Individual staff members also participated in a number of technical design, development and implementation tasks to address the data management and statistical computing requirements of the overall Program. Technical assistance and support for personal computer services continued to command staff resources. A staff member continued to serve as the Program's Executive Secretary responsible for the procurement, management and monitoring of research and resource contracts. In addition, a variety of audio-visual materials was prepared for presentations given by Program researchers, an inventory of all Program hardware and commonly used software was maintained, and a system was designed to report on the demographic and socioeconomic composition of all Program study cohorts.

SUMMARY REPORT
BIOSTATISTICS BRANCH
PROGRESS ON RESEARCH CONTRACTS

The Branch's research contracts (FY-91 expenditures \$182,000) support unique or rare opportunities to study populations with unusual risk patterns and exposures to understand better the etiology of certain cancers.

To evaluate risk factors in high cancer rate areas and in heavily exposed populations in China, collaborative contracts continued with the Chinese Academy of Medical Sciences (CAMS), the Chinese Academy of Preventive Medicine (CAPM), and the Beijing Institute for Cancer Research (BICR).

The CAMS contract (CP-05634) enables the conduct of a 6-year randomized intervention trial in Linxian to test whether vitamin/mineral supplementation can lower the incidence of esophageal cancer, which occurs more commonly in this rural county than elsewhere in the world. Over 33,000 persons are enrolled, and monitoring of their cancer experience continues. Contract CP-85641 with the CAPM supports a cohort survey evaluating risks from benzene among approximately 100,000 workers in 12 Chinese cities. Air monitoring data from factories are being used to classify workers according to benzene exposure, and follow-up for mortality is nearing completion. A contract with the BICR (CP-15620) enables the conduct of a survey of 3,000 high-risk subjects to classify gastric lesions, identify their determinants, and chart changes to cancer over time.

BIostatistics BRANCH
RESEARCH CONTRACTS ACTIVE DURING FY-91

Institution/Principal Investigator
Contract Number

Title

Chinese Academy of Medical Sciences
Dr. Li Bing
N01-CP-05634

Nutrition Intervention Trial
in Linxian China

Chinese Academy of Preventive Medicine
Dr. Yin Songnian
N01-CP-85641

An Epidemiologic Study of
Benzene Exposure in China

Beijing Institute for Cancer Research
Dr. You Wei-cheng
N01-CP-15620

Precancerous Gastric
Lesions: Study of Their
Determinants and Rates
of Transition in a
Population in China at
High Risk of Stomach
Cancer

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04265-26 BB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Consulting in Statistics and Applied Mathematics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: J.J. Gart Chief, MSAMS BB NCI

Others: R.E. Tarone Mathematical Statistician BB NCI
D.G. Thomas Mathematical Statistician BB NCI
J. Nam Mathematical Statistician BB NCI

COOPERATING UNITS (if any)

NONE

LAB/BRANCH

Biostatistics Branch

SECTION

Mathematical Statistics and Applied Mathematics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS: 2.0

PROFESSIONAL: 2.0

OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

It is the purpose of this study to collaborate with NCI researchers on mathematical problems related to many areas of cancer research. Consulting assistance in statistical methodology and applied mathematics is provided for NCI investigators and to some extent for NCI contractors. In general, the study is devoted to accelerating the use of quantitative methodology in various aspects of the NCI intramural and extramural programs.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J.J. Gart	Chief, MSAMS	BB	NCI
R.E. Tarone	Mathematical Statistician	BB	NCI
D.G. Thomas	Mathematical Statistician	BB	NCI
J. Nam	Mathematical Statistician	BB	NCI

Objectives:

The principal objectives are (1) to collaborate with NCI scientists on mathematical problems related to cancer research, (2) to provide consulting assistance in statistics and applied mathematics to NCI investigators, and (3) to accelerate the use of quantitative methodology in various aspects of the NCI intramural program and extramural program.

Methods Employed:

The methodology of applied mathematics, mathematical statistics and probability is applied to biomedical problems. Often various variations of existing techniques are developed to suit the special requirements of a particular problem.

Major Findings:

During this year, the staff advised and collaborated with many investigators in the major research divisions in the National Cancer Institute, as well as some contractors and investigators elsewhere. The various projects are grouped below in terms of the divisions and areas of the projects.

Division of Cancer Etiology - Epidemiology and Biostatistics Program

Dr. Tarone and Dr. Howard Hayes of the Environmental Epidemiology Branch continue their investigation of Vietnam service as a possible risk factor for testicular cancer. They have reanalyzed a case-control study of testicular cancer in man and have completed a paper reporting a twofold increased risk in Vietnam veterans. Dr. Tarone and Dr. Hayes have obtained medical records for military working dogs which served during the Vietnam conflict and are continuing their investigation into the increased risk of testicular tumors in dogs with Vietnam service.

Dr. Gart and Mr. Nam collaborated with Dr. Pottorn of the Environmental Epidemiology Branch on a study to investigate the association of the HLA system with multiple myeloma in both blacks and whites. The paper reporting the findings is in preparation.

Mr. Nam, Drs. Blot and McLaughlin of the Biostatistics Branch have conducted a case-control study of nasopharyngeal cancer to identify risk factors from the National Mortality Followback Survey. They have completed the paper reporting the risk

factors for this cancer and are planning a similar case-control study of pituitary cancer.

Dr. Tarone completed collaboration with Dr. Howard Hayes and Dr. Kenneth Cantor of the Environmental Epidemiology Branch on a case-control study of canine malignant lymphoma. They have completed a manuscript reporting a significantly increased risk in dogs whose owners applied 2,4-D or used a commercial lawn care service.

Mr. Thomas continues to provide support on computer software and hardware to various members of the section and branch. Numerous researchers throughout the world request and use software developed in this section.

Dr. Tarone continues to collaborate with Dr. John Boice and Ms. Ruth Kleinerman of the Radiation Epidemiology Branch in studies quantifying the persistence of chromosome aberrations in individuals receiving therapeutic exposures to ionizing radiation several decades previously. They are also examining the efficacy of using rates of stable chromosome aberrations in peripheral blood lymphocytes or somatic mutations at the glycophorin A locus as dosimeters for chronic exposure to low doses of ionizing radiation in a study of nuclear power plant workers in Sellafield, U.K.

Dr. Tarone continued to assist Dr. Martha Linet of the Biostatistics Branch and Dr. John Boice of the Radiation Epidemiology Branch in planning a case-control study to evaluate the possible relationship between electromagnetic field exposure and risk of childhood leukemia.

Dr. Tarone is collaborating with Dr. John Boice of the Radiation Epidemiology Branch in a study of the children of radiological technologists to determine if preconceptional or prenatal exposure to ionizing radiation is associated with increased risk of leukemia.

Dr. Tarone continues to assist Dr. Paul Levine and Ms. Elizabeth Maloney of the Environmental Epidemiology Branch in their studies of Gm immunoglobulin allotypes and possible associations with HTLV-I infection or HTLV-I associated diseases, such as adult T-cell leukemia and HTLV-I associated myelopathy.

Dr. Tarone assisted Dr. Deoraj Caussy of the Environmental Epidemiology Branch in the statistical analysis of a study to determine risk factors for HIV infection in a cohort of homosexual men. Dr. Tarone also performed power calculations for Dr. Caussy relating to a study of HTLV-I and HPV prevalence in Jamaica, and possible associations of virus infection with cervical cancer risk.

Donald G. Thomas advised Mitchell Gail, Chief, Epidemiology Methods Section on the selection of new microcomputers for his section.

Division of Cancer Etiology - Other Programs

Dr. Tarone completed collaboration with Dr. Kenneth Kraemer of the Laboratory of Molecular Carcinogenesis and Ms. Susanna Barrett of the Dermatology Branch in the Division of Cancer Biology, Diagnosis, and Centers on experiments designed to differentiate the DNA repair defects of Cockayne's syndrome and xeroderma pigmentosum, and a paper reporting the results of this study has been submitted.

Dr. Tarone continued to assist Dr. Kraemer in the evaluation of a study assessing the efficacy of isotretinoin in preventing skin tumors in xeroderma pigmentosum patients.

Dr. Gart collaborated with Dr. Richard Burt of the Laboratory of Experimental Carcinogenesis on the analysis of a study of the effect of partial pressure of carbon dioxide on the canine coronary sinus blood flow and myocardial infarct size. A paper on the results will soon be published.

Dr. Tarone continues to collaborate with Dr. Katherine Sanford of the Laboratory of Cellular and Molecular Biology in studies examining increased susceptibility to radiation-induced chromatid damage in cells from patients with cancer-prone diseases. He is also assisting Dr. Sanford and Dr. Jay Robbins of the Dermatology Branch of the Division of Cancer Biology, Diagnosis, and Centers in devising a cytogenetic test for carriers of the gene for Alzheimer's disease.

Dr. Tarone collaborated with Dr. Miriam Poirier of the Laboratory of Cellular Carcinogenesis and Tumor Promotion and Dr. Eddie Reed of the Clinical Oncology Program of the Division of Cancer Treatment in studies designed to determine if there is a direct association between response to cisplatin treatment and the level of platinum-DNA adducts induced in peripheral leukocytes of cancer patients.

Dr. Tarone performed statistical analyses for Dr. Monica Hollstein and Dr. Curt Harris of the Laboratory of Human Carcinogenesis in a study of the distribution of point mutations in the p53 tumor suppressor gene to determine if the spectrum of base substitutions varied among cancers at different sites, and if mutations occurred more frequently at highly conserved regions of the gene.

Dr. Tarone performed statistical analyses for Dr. Ulrike Lichti of the Laboratory of Cellular Carcinogenesis and Tumor Production to assess variations in enzyme (TGASE) levels in cultured cells with different cytokines or treatments.

Division of Cancer Biology, Diagnosis and Centers

Dr. Gart collaborated with Dr. Kari Irvine of the Laboratory of Tumor Immunology and Biology on the analysis of a series of animal experiments evaluating antigen positive tumor cells and test hybridoma cells.

Dr. Tarone continues his collaboration with Dr. Jay Robbins and others in the Dermatology Branch in experiments examining in vitro sensitivity of cultured cells from patients with cancer-prone diseases and primary neuronal degenerations after exposure to DNA-damaging agents, in order to assess the possible role of defective DNA repair in carcinogenesis and neurodegeneration.

Division of Cancer Treatment

Dr. Tarone performed statistical analyses for Dr. Albert Fornace of the Laboratory of Molecular Pharmacology in experiments performed to identify genes inducible by ionizing radiation in cultured human cells and to examine factors related to gene expression.

Other Government Agencies

Mr. Thomas advised Hugh Pettigrew of the Environmental Protection Agency on statistical software developed in this section.

Publications:

Burt RK, Parnis SM, Nakatani T, Gart JJ, Diek JA, Ferguson JJ. The effect of partial pressure of carbon dioxide on canine coronary sinus blood flow. *J Appl Cardiol* (In Press).

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Sanford KK, Parshad R, Tarone RE. A deficiency in chromatin repair, genetic instability and predisposition to cancer. *Crit Rev Oncogen* 1989;1:323-41.

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Z01CP04265-26 BB

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04267-26 BB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Research in Statistics and Applied Mathematics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	J.J. Gart	Chief, MSAMS	BB	NCI
Others:	R.E. Tarone	Mathematical Statistician	BB	NCI
	D.G. Thomas	Mathematical Statistician	BB	NCI
	J. Nam	Mathematical Statistician	BB	NCI

COOPERATING UNITS (if any)

NONE

LAB/BRANCH

Biostatistics Branch

SECTION

Mathematical Statistics and Applied Mathematics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS: 2.0

PROFESSIONAL: 2.0

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CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

It is the purpose of this project to conduct research in mathematical statistics, probability, and applied mathematics, and especially to develop new statistical methodology which is applicable to the biomedical sciences. Particular subjects of interest are the methodology of analyzing survival curves and proportions, and statistical methods in cancer epidemiology and statistical genetics.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. J. Gart	Chief, MSAMS	BB	NCI
R. E. Tarone	Mathematical Statistician	BB	NCI
D. G. Thomas	Mathematical Statistician	BB	NCI
J. Nam	Mathematical Statistician	BB	NCI

Objectives:

To conduct research in mathematical statistics, probability, and applied mathematics; to develop new statistical methodology which is especially appropriate to biomedical sciences.

Methods Employed:

The methods employed are the modern theories of mathematical statistics, probability, and applied mathematics. High speed electronic computers are often used to compute appropriate mathematical tables, to test approximations by simulation techniques, and to do exact permutational analyses.

Major Findings:

The research of the members of this section covers a wide spectrum of topics in mathematical statistics, probability, and applied mathematics. These are summarized below.

John J. Gart has completed his research on the effects of pooling over covariates on such commonly used measures of association as the odds ratio, relative risk, and difference in proportions. It is shown that Armitage's test for heterogeneity of proportions may be used to test for validity of such pooling of categorical data. The results are included in two papers soon to be published. John J. Gart and Donald G. Thomas are studying new point and interval estimates of the attributable risk. These estimators, unlike those previously proposed, are both efficient and symmetric with regard to the exposure variable.

Donald G. Thomas, in conjunction with John J. Gart, is incorporating these novel methods into a sophisticated computer program for stratified data. This program uses exact and other more accurate approximate techniques developed in this Section to compute point and interval estimates, as well as interaction tests, for the odds ratio and attributable risk. Also included is a test for pooling.

John J. Gart has completed his research on the appropriate statistical test for comparing neighborhood and hospital controls in matched case-control studies. A paper on these results will be published shortly. Research in progress includes the calculation of the appropriate P-values in sequential clinical trials, with Dr. William Blackwelder of the National Institute of Allergy and Infectious Diseases, on sample size determination in testing the null hypothesis of relative risk less than unity where skewness of the distribution may be an important factor.

Robert E. Tarone continues investigations into statistical methods for sparse data situations such as those arising from the analysis of the distribution of mutations induced in a gene of known sequence and of the distribution of chromosome aberrations among bands in banded chromosome preparations. He is attempting to develop an omnibus homogeneity test with improved power when data are sparse.

Robert E. Tarone continues research on methods for analyzing survival curves produced by *in vitro* exposure of cultured cells to DNA-damaging agents, methods for the statistical analysis of Gm immunoglobulin allotype data, and consequences of multiple analyses and multiple comparisons in the analysis of epidemiologic studies.

Jun-mo Nam has completed his research on refined sample size formulas for designing case-control studies and, together with Thomas Fears of the Biostatistics Branch, has completed research on optimal sample size determination in stratified case-control studies with cost considerations. Two papers based on these results have or will soon be published. Related work involves sample size problems in estimating a common difference in proportions and other design problems in stratified discrete data. Other topics under investigation include statistical methods in genetic models and estimation problems in bioassay and stratified regression.

Donald G. Thomas provides computer advice and support for several of the research topics reported here.

Publications:

Gart JJ. An application of score methodology: confidence intervals and tests of fit for one-hit curves. In: Rao CR, Chakraborty R. eds. Handbook of statistics, vol. 8. statistical methods for biological and medical sciences. Amsterdam: North-Holland (In Press).

Gart JJ. The identity of Armitage's two tests of heterogeneity of proportions for proportional subclass numbers. J Roy Statist Soc B (In Press).

Gart JJ. Pooling 2x2 tables: asymptotic moments of estimators. J Royal Stat Soc B (In Press).

Gart JJ. Simple tests of homogeneity of controls in matched studies. Stat Med (In Press).

Gart JJ, Nam J. Approximate interval estimation of the difference in binomial parameters: correction for skewness and extension to multiple tables. Biometrics 1990;46:637-43.

Nam J. Non-iterative estimator of common difference in binomial parameters in multiple 2x2 tables and score test for homogeneity of differences. Proceedings of the eleventh Korea symposium on science and technology: Mathematics and statistics. Seoul: Korea Federation of Science and Engineering Associations, 1990:51-6.

Nam J. Sample size determination for case-control studies and the comparison of stratified and unstratified analyses. Biometrics (In Press).

Z01CP04267-26 BB

Nam J, Fears TR. Optimum allocation of samples in strata-matching case-control studies when cost per sample differs from stratum to stratum. Stat Med 1990;9:1475-83.

Tarone RE. A modified Bonferroni method for discrete data. Biometrics 1990;46:515-22.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04269-20 BB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Biomedical Computing - Consultation, Research and Development Service

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: J.M. Stump Chief, IRMS BB NCI

Others: D.J. Grauman Computer Systems Analyst BB NCI
R.I. Ramsbottom Computer Specialist BB NCI
B.L. Stephenson Computer Specialist BB NCI
C.R. Whitney Computer Aide BB NCI
R.S. Wolfson Computer Programmer/Analyst BB NCI

COOPERATING UNITS (if any)

NONE

LAB/BRANCH

Biostatistics Branch

SECTION

Information Resources Management Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS: 6.0

PROFESSIONAL: 5.0

OTHER: 1.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Information Resources Management Section executes a broad program of computer-related consultation and services focused on support to all areas of the Epidemiology and Biostatistics Program. Support is provided to other organizations within the Division of Cancer Etiology upon request. The Section's mission includes: 1) planning and conducting research and development work to improve methodology in the application of computers and data processing techniques in support of research conducted and coordinated by NCI investigators and their collaborators; 2) serving as the focal point in the Epidemiology and Biostatistics Program for the procurement, management and monitoring of support services contracts, and for the evaluation and procurement of automatic data processing and word processing equipment as well as data resources used by staff investigators; 3) providing liaison, consultation and collaboration to NCI investigators on the design, development and operation of data processing and information systems; and 4) representing the Division of Cancer Etiology in providing consultation, guidance and assistance to the National Cancer Institute and the Division of Computer Research and Technology (DCRT) on ADP and office automation issues, problems and operations.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J.M. Stump	Chief, IRMS	BB	NCI
D.J. Grauman	Computer Systems Analyst	BB	NCI
R.I. Ramsbottom	Computer Specialist	BB	NCI
B.L. Stephenson	Computer Specialist	BB	NCI
C.R. Whitney	Computer Aide	BB	NCI
R.S. Wolfson	Computer Programmer/Analyst	BB	NCI

Objectives:

To provide computer-related consultation, liaison and collaboration to NCI investigators and to other Government agencies, private institutions and individual investigators who collaborate with the National Cancer Institute. Emphasis is placed on providing support for the design, development and operation of data management, computer statistical analysis and information and reporting systems for a large program of epidemiological and biostatistical research. Overall coordination is provided for the management of various computer support services obtained under contract, for the procurement of other Epidemiology and Biostatistics (E&B) Program research and resource contracts and for the acquisition and utilization of various information resources and automatic data processing equipment used by the staff of the E&B Program. Research and development studies are conducted to improve methodology in the application of computers and data processing techniques in support of scientific research conducted by the E&B Program.

Methods Employed:

The staff of the Information Resources Management Section (IRMS) utilizes a variety of analytical, technical and administrative skills to execute a broad program of consultation, service and support for research projects having data management and statistical computing requirements. The primary focus of Section activities is the support of Epidemiology and Biostatistics Program projects; however, other projects from throughout the NCI and NIH receive support when resources permit. In addition, resulting technologies, methodologies and data resources are shared with other government agencies and the extramural community.

The major recurring activities of the Section include contract procurement and administration, information management and dissemination, and technical systems design to develop new and improved methodology in the application of computers to cancer research and related activities.

Major Findings:

This year, major activities of the Section included: 1) extending present efforts to contain the costs for DCRT computing services; 2) planning for extended Local Area Network coverage; 3) preparing for the release of the 1990 census data; and 4) participating in a number of technical design, development and implementation tasks

to address the data management and statistical computing requirements of the E&B Program.

The Section's activities aimed at effecting cost reductions in DCRT computing costs extended beyond E&B Program staff and their computer support contractors to include the two large general support services organizations under contract to the E&B Program. An aggressive campaign to cut DCRT-related costs was initiated focusing on more efficient data storage techniques, increased use of personal computers and more comprehensive reporting to monitor progress towards meeting cost containment goals.

The Local Area Network (LAN) continues to proliferate throughout the E&B Program with 34 additional workstations being planned. Activities are also being directed towards establishing LAN links with all other DCE organizations located in Executive Plaza North. It is anticipated that interest in the LAN facility will increase dramatically since hookups have been recently established in all DCE administrative offices and the Office of the Director, DCE.

The Bureau of the Census is scheduled to release the 1990 census figures in the Fall of 1991. IRMS staff have started the planning and coordination required to update the existing rate files used with various analytical software packages, mapping routines and specialized analyses to insure consistency, compatibility and comparability with previously conducted analyses and published results.

The Biospecimen Inventory System, a standardized protocol for collecting, storing and disseminating biospecimen materials, is being implemented at another repository participating in the E&B Program. Plans are also being made to adapt it for use at the new repository scheduled for operation at the Frederick Cancer Research and Development Center.

Staff of the IRMS is leading an effort to systematically review, redesign and develop several of the larger systems used to support the research program of the Family Studies Section (FSS). After a preliminary analysis of all major systems used by Environmental Epidemiology Branch (EEB) investigators, it was determined that the FSS systems were the most technologically outdated and difficult to operate and, in addition, were least responsive to the current needs of the researchers. Staff from the Environmental Epidemiology Branch's computer support contract are participating in this ambitious endeavor.

Individual staff members continued to provide support to new and ongoing projects. Technical assistance and support for personal computers continued to command staff resources with new requests for support coming from the Office of the Director, DCE as well as from other DCE branches and laboratories. A variety of audio-visual materials was prepared for presentations given by Program researchers, an inventory of all E&B Program hardware was maintained, software packages with potential application to the Program's research needs were evaluated and a system was designed to report on the demographic and socio-economic composition of all E&B Program study cohorts.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04475-14 BB

PERIOD COVERED

October 1, 1990 through September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Skin Cancer and Solar Radiation Program

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: J. Scotto Health Services Director BB NCI

Others: T.R. Fears Mathematical Statistician BB NCI
J.F. Fraumeni, Jr. Associate Director E&B NCI

COOPERATING UNITS (if any) National Oceanic and Atmospheric Administration (G. Cotton, J. DeLuigi); EPA (H. Pitcher); U. Washington (J.A.H. Lee); Dartmouth (R. Greenberg); Temple U. (F. Urbach, D. Berger); U. Chicago (J. Frederick); George Wash. U. (F. Noonan, E. DeFabo); Georgia Tech (C.G. Justus); Office of Science and Technology Policy (J. Chow).

LAB/BRANCH

Biostatistics Branch

SECTION

Analytical Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

1.1

PROFESSIONAL:

1.1

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Physical measurements of solar ultraviolet radiation (UVB) and epidemiological data on skin cancer, including malignant melanoma, are collected and analyzed. These studies supply scientific evidence related to the potential consequences of continued ozone depletion and climate change (i.e., global warming), and thus may help develop policy relative to man-made atmospheric pollutants and international agreements to ban their use, such as the Montreal Protocol. Despite reports of recent stratospheric ozone depletion detected by satellites, our surface-based measurements of solar ultraviolet radiation of 290nm to 330nm wavelengths (UVB) continue to show no increasing trends at urban locations within the United States. The results also agree for rural areas, across continents, and in both hemispheres. For several U.S. locations, trends in incidence and mortality rates for malignant skin melanoma are compared with annual and monthly variations in solar UVB flux. Though UVB exposure is associated with increased risk, changes in stratospheric ozone depletion do not appear to be responsible for recent worldwide increases in the incidence of melanoma and skin cancer. Age and cohort analyses of skin melanoma mortality rates indicate that males born during the 1950s, and females born during the 1930s were at highest risk. Decreasing trends were noted among young cohorts and age groups under 30. Without additional increases in UVB exposure, age-adjusted skin melanoma mortality rates are projected to decline early in the 21st century.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on the Project:

J. Scotto	Health Services Director	BB NCI
T. R. Fears	Mathematical Statistician	BB NCI
J.F. Fraumeni, Jr.	Associate Director	E&B NCI

Objectives:

The major objectives of this study are to provide epidemiologic data relative to the etiology of skin cancer, including malignant melanoma and to evaluate the potential human health effects of harmful solar ultraviolet radiation (UVB, i.e., wavelengths between 290 nm and 320 nm). In particular studies are (1) to provide measurements of solar ultraviolet exposure necessary to ascertain the human health effects of ultraviolet (UV) radiation resulting from anticipated ozone depletions in our biosphere; (2) to provide basic data to reduce the degree of uncertainty in dose-response estimators; (3) to provide specific host and environmental data on populations suspected to be at high or low risk of skin malignancy; (4) to provide an estimate of the proportion of skin cancer in the community relative to other cancers; (5) to identify local factors in the community; (7) to provide basic epidemiologic data to elucidate the multifactorial etiology of skin cancer; (8) to estimate trends in skin cancer morbidity and mortality; and (9) to develop dose-response models which may explain initiator/promoter factors associated with UVB radiation exposure.

Methods Employed:

Photobiologic measurements of UVB are obtained at 20 geographic locations throughout the United States and several foreign stations. In the U.S., the locations range in latitude from 19.5 (Mauna Loa, Hawaii) to 71.3 (Point Barrow, Alaska) degrees north. At several stations, daily readings have been monitored since 1974, and NCI's analytical data base now spans over 16 years at Albuquerque, New Mexico, and Mauna Loa, Hawaii. NCI has collaborated with the National Oceanic and Atmospheric Association Administration (including its network of weather stations) and Temple University (developers of the Robertson-Berger UVB meter) in obtaining, monitoring, calibrating, editing, and analyzing ground level readings of solar ultraviolet radiation. The direct measurements obtained from ground level R-B meters are internally weighted for UVB wavelengths between 290nm and 330nm according to an erythema (sunburn) action spectrum. The minimal erythema dose (MED) for the average, untanned Caucasian skin is equivalent to approximately 30 mJ/cm². Time series analyses are employed to measure UV-B trends and to compare diurnal, monthly, and annual patterns with other meteorological factors, such as tropospheric and stratospheric ozone, total solar radiation, cloud cover, and atmospheric levels of sulphur dioxide (SO₂), nitrogen oxides (NO_x), and carbon dioxide (CO₂).

Currently, there are a dozen stations where population-based morbidity surveys were conducted for skin cancer or skin melanoma; and seven of these are participating in NCI's continuing Surveillance, Epidemiology, and End Results (SEER) Program. The National Center for Health Statistics (NCHS) records were utilized to develop skin melanoma and nonmelanoma skin cancer mortality rates from 1950 to present. Census data are used to provide detailed population estimates specific for age, race, ethnicity, sex and geographic location.

Major Findings:

Extending time series analyses through mid-1990 for Albuquerque, New Mexico, and Mauna Loa, Hawaii, we found no statistically significant trends in monthly measurements of surface levels of UVB. We have found agreement in UVB trends across continents and in the southern hemisphere. This is in contrast to trends from satellite data which show global stratospheric ozone depletion (and estimated UV increases) during similar time spans. Our research has prompted investigations of the influence of UVB-absorbing particulates in the atmosphere, especially in urban areas with relatively high air pollution. Recent studies indicate that the effects of UVB-absorbing sulfur dioxide in the atmosphere may overshadow small relative changes in ozone. Analyses of half-hourly measurements of UVB on clear days (to eliminate cloud effects) at Mauna Loa since 1974 were made to evaluate the precision of reported calibration factors, and to compare trends with total solar radiation measurements. Calibration factors for the UVB instrument through 1985 were in agreement with estimates derived from total solar radiation measurements. At locations where both UVB and ozone data are available, we observed that huge drops in monthly ozone levels are associated with increases in UVB readings. Our findings indicate recent stratospheric ozone depletions do not explain increases in skin cancer incidence, including melanoma, which began over 50 years ago.

Age and cohort analyses of skin melanoma mortality rates among whites in the United States (1950 to 1984) show that males born during the 1950s and females born during the 1930s may be at highest risk. In contrast to upward trends observed for older men and women, downward trends were noted for younger age groups. After adjusting for cohort and age effects and assuming no additional increases in solar ultraviolet radiation exposure, skin melanoma mortality rates are projected to begin to decrease by the year 2010. Results from this study may be utilized to improve estimates of the potentially harmful effects of continued ozone depletion into the next century.

Nonmelanoma skin cancer mortality rates, which had steadily declined between 1950 and 1970, remained at about the same level of about 1.0 per 100,000 population during the 1970s, then apparently increased during the 1980s. By 1986 the age-adjusted rate for nonwhite males (1.4) was about equal to that observed for white males. Detailed analyses of age-race-sex trends traced the increases to Kaposi's sarcoma, a skin malignancy frequently seen among AIDS cases, and to changes in classification of death certificate codes.

While skin cancer, including melanoma, incidence is seen to peak during the summer months, i.e., when solar ultraviolet radiation is also at its highest

intensity level, this association could not be found for other sites, such as breast and colon cancer.

Within the United States, the average daily amount of UVB reaching Hawaii, our southernmost state, exceeds that received in Alaska, our northernmost state, by a factor of 9. There are enormous differences between solar seasons; but, minimal erythema (sunburn) doses may be received at any geographic location during the summertime between the hours of 10:00 a.m. and 2:00 p.m. When the zenith angle (i.e., $Z=0^\circ$ as the sun is directly overhead, and $Z=90^\circ$ at the horizon) exceeds 45° , usually between 3:00 p.m. and 4:00 p.m., the amount of UVB reaching the earth's surface is insufficient to cause sunburn to the average Caucasian skin.

Skin cancer incidence rates among whites in the combined states of New Hampshire and Vermont and surface measurements of UVB at Concord, N.H., and Burlington, VT., were found consistent with dose-response model estimates previously reported. The caucasian population in this northeastern region of the United States was at lower risk, relative to other northern and southern regions, but the proportion of patients with a prior history of basal cell or squamous cell carcinoma of the skin was relatively high and increased progressively with age.

Publications

Scotto J, Fears TR, Fraumeni JF, Jr. Solar ultraviolet radiation effects. In: Schottenfeld D, Fraumeni JF, Jr. eds. Cancer epidemiology and prevention. 2nd ed. New York: Oxford Univ Press (In Press).

Scotto J, Pitcher H, Lee JAH, Fraumeni, JF, Jr. Indications of future decreasing trends in skin melanoma among whites in the United States. Int J Cancer (In Press).

Serrano H, Scotto J, Shornick G, Fears TR, Greenberg ER. Incidence of nonmelanoma skin cancer in New Hampshire and Vermont. J Am Acad Dermatol 1991; 24:575-9.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01CP04500-14 BB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Methodologic Studies of Epidemiology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	M.H. Gail	Head, Epidemiologic Methods Section	BB	NCI
Others:	W.J. Blot	Chief, Biostatistics Branch	BB	NCI
	T.R. Fears	Mathematical Statistician	BB	NCI
	R.J. Carroll	Visiting Statistician	BB	NCI
	J.G. Benichou	Epidemiol. & Biostat. Training Fellow	BB	NCI
	J.H. Lubin	Health Statistician	BB	NCI
	P.S. Rosenberg	Staff Fellow	BB	NCI
	S. Wacholder	Senior Staff Fellow	BB	NCI
	J.K. McLaughlin	Epidemiologist	BB	NCI

COOPERATING UNITS (if any) Johns Hopkins U., Baltimore (R. Brookmeyer); NIEHS, Research Triangle Park (C. Weinberg); New Mexico Tumor Registry, Albuquerque (J. Samet); NIAID (S. Machado); Texas A&M U. (F. Dahm); U. of Minnesota (J.S. Mandel); U. of Pittsburgh (J. Mulvihill); NCHS, Hyattsville (G.S. Poe); Columbia U., New York (W-Y. Tsai); Radiat. Effects Res. Foundation, Japan (D. Preston)

LAB/BRANCH

Biostatistics Branch

SECTION

Epidemiologic Methods Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

3.3

PROFESSIONAL:

2.9

OTHER:

0.4

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

New methods are being developed to incorporate treatment effects into models for determining HIV seroprevalence and projecting AIDS incidence by backcalculation, and publications have appeared on rapid flexible methods of backcalculation and on the reliability of estimates of seroprevalence and AIDS incidence projections obtained by backcalculation. Work on the use of surrogate markers in clinical trials to treat HIV infection and work on other aspects of such clinical trials have been published. Work on the effects of errors in measurements of exposure indicates that unexpected biases away from the null hypothesis can arise, even when errors are nondifferential, if exposures are polychotomous. Extensions show that combining exposure categories in this setting can lead to biases away from the null hypothesis or even reverse the direction of an association, and similar results were obtained for clinical trials in which the endpoint is a composite of several component clinical categories. Manuscripts have been prepared describing new methods of analysis of case-control data that incorporate validation sampling to relate surrogate exposures to "gold standard" exposures, and that use an initial validation sample to design the size of a subsequent larger sample using only surrogate exposure data. Work on the reliability of next-of-kin interview data and comparisons with death certificate information are in press. Methods for selecting controls for case-control studies have been reviewed, and papers have appeared on the weighted selection of controls and on optimal allocation of controls when the costs of obtaining controls vary across strata. Appropriate logistic analyses have been developed for controls obtained by cluster sampling. Two papers describing practical and theoretical issues in selecting a design for studying a large assembled cohort appeared. Papers appeared on the analysis of attributable risk based on logistic regression and on estimates of absolute risk from cohort studies. Related work for population-based case-control studies is in progress.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

M.H. Gail	Head, Epidemiologic Methods Section	BB	NCI
W.J. Blot	Chief, Biostatistics Branch	BB	NCI
T.R. Fears	Mathematical Statistician	BB	NCI
J.H. Lubin	Health Statistician	BB	NCI
P.S. Rosenberg	Senior Staff Fellow	BB	NCI
S. Wacholder	Senior Staff Fellow	BB	NCI
D.T. Silverman	Epidemiologist	BB	NCI
J.D. Boice	Chief, Radiation Epidemiology Branch	REB	NCI
D.P. Byar	Chief, Biometry Branch	DCPC	NCI
J. Nam	Mathematical Statistician	BB	NCI
B. Graubard	Mathematical Statistician	DCPC	NCI
R.J. Carroll	Visiting Statistician	BB	NCI
J.G. Benichou	Epidemiol. & Biostat. Training Fellow	BB	NCI
J.K. McLaughlin	Epidemiologist	BB	NCI

Objectives:

To develop, adapt, and evaluate methodologic procedures useful in epidemiologic studies of cancer. Emphasis is placed on statistical and operational methods for the design, implementation, interpretation and analysis of a broad range of human studies, including both observational and experimental designs.

Methods Employed:

A variety of techniques are applied, including the formulation and testing of epidemiologic procedures, such as the use of surrogate controls, the development and use of computer algorithms, and reliance on the methods of biostatistics and mathematical analysis. These methods are applied to data generated by investigators in the Biostatistics Branch and other branches within the Epidemiology and Biostatistics Program, and elsewhere.

Major Findings:

Work continues on methods for selecting controls and other aspects of the design and analysis of case-control studies. Branch members, in collaboration with Dr. J. Mandel of the University of Minnesota, have written an extensive three-part review of the theory and practice of selecting controls. The review emphasizes selecting controls from an appropriate base population and also discusses aspects of comparability and design options, including stratification. Methods for weighted selection of controls, in which the probability of selection depends both on case-control status and on the level of some easily determined covariate, such as whether or not the subject is currently smoking, were developed in collaboration with Dr. C. Weinberg of the National Institute of Environmental Health Sciences and published. Branch staff have considered efficient allocation of controls to strata when the costs of obtaining controls differ among strata. One paper appeared describing how to achieve maximal statistical efficiency with fixed costs. A second paper has been

submitted describing sample sizes needed to achieve given power for allocation ratios designed to minimize cost, and a third paper is in preparation to define sampling sizes needed to achieve specified precision using allocation ratios designed to minimize cost. Dr. B. Graubard, of the Division of Cancer Prevention and Control (DCPC), and Branch staff have completed theoretical work permitting a complete logistic analysis of case-control data in which controls are selected as cluster samples, and a manuscript is in preparation.

Several staff members have been working on the development of efficient designs and methods of analysis for large cohorts. A paper was published showing how to select the most efficient method of sampling controls from a large assembled cohort. Several sampling options were considered, including case-cohort and nested case-control sampling. An expository paper appeared that compares theoretical and practical advantages and disadvantages of these designs. Work continues on methods for Poisson regression of case-cohort data.

Branch staff have studied several aspects of the effects of errors in exposure measurements on the design and analysis of epidemiologic studies. A paper was written to review available methods and develop new analytical methods for case-control studies. That paper gives corrected estimates of relative risk derived from surrogate exposure measurements by using validation data that relate "gold standard" exposure measurements to disease outcome and to surrogate exposure measurements. A related manuscript has been prepared showing how an initial sample of validation data can be used to determine the value of subsequent data on disease outcome and surrogate exposure only. Such calculations can be used to select an appropriate sample size for the surrogate exposure data sample. In collaboration with staff in the Occupational Studies Section, Branch members have published a paper showing that if exposures are polychotomous, some odds ratios may be biased towards the null hypothesis and others away from it, even if measurement errors are the same among cases and controls (nondifferential error). Related work in press shows that collapsing adjacent polychotomous exposure categories in the presence of nondifferential error can lead to differential misclassification in the collapsed categories, bias away from the null hypothesis, or even reversal of the direction of estimated treatment effects. Likewise, a paper in press demonstrates that such biases can occur in clinical trials when the endpoint is a composite indicator of several component conditions, even though "blinded" assessment assures nondifferential error structure for each component condition. An example would be the endpoint of an AIDS diagnosis, which occurs when any of several component disease criteria have been met.

One published paper describes the quality of data on smoking, coffee and alcohol exposures obtained from interviews of next-of-kin, and another is in press describing the relationship between the delay between the death of a subject and the interview of next-of-kin and the quality and completeness of data obtained. Two papers are in press indicating that death certificate data and data from next-of-kin interviews agree well (>90%) for demographic variables, such as age and race, but less well (70%) for determination of work history, including industry and occupation.

Section staff have written several papers on risk assessment in epidemiologic studies. A paper appeared on how to calculate confidence intervals for the

attributable risk based on a logistic analysis of case-control data, and work is underway to develop computer programs and to apply these methods to the analysis of a case-control study of bladder cancer. A review and comparison of several recent methods of analysis for attributable risk has also been submitted for publication. A paper appeared showing how to estimate and perform statistical inference for the absolute risk of disease in cohort studies. Current work is extending methods of inference for the absolute risk to population based case-control studies, and these methods will be applied to obtaining more realistic assessments of uncertainty when projecting the probability (absolute risk) that a woman with given risk factors will develop breast cancer in a given time interval. In collaboration with Dr. J. Mulvihill (University of Pittsburgh), these methods are being incorporated into an expository paper on projection of individualized risk of breast cancer.

A number of new methods have been developed for studying the AIDS epidemic and related clinical trials. A paper on rapid flexible regression methods of backcalculation appeared, as well as an assessment of the uncertainties in estimating human immunodeficiency virus (HIV) seroprevalence and projecting AIDS incidence from backcalculation. Related simulation studies to determine the reliability of backcalculation methods for various possible epidemic infection curves are in press. Ongoing theoretical work incorporates the extent and effectiveness of treatment and changes in the definition of AIDS into backcalculation methods to make them useful in the 1990s. Two papers with Dr. R. Brookmeyer (Johns Hopkins University) addressed evolving statistical issues, including the need to incorporate treatment effects when projecting AIDS incidence. Methods for estimating hazard functions based on splines are in development for use in detecting treatment induced changes in the hazard function in a cohort of patients with hemophilia and an international registry of seroconverters. In collaboration with Dr. W.-Y. Tsai of Columbia University and staff in the Viral Epidemiology Section of the Environmental Epidemiology Branch, methods are being developed to obtain unbiased estimates of the probability of perinatal transmission of HIV. One approach assumes uninformative censoring, and another approach takes into account the last HIV antibody measurements before loss to follow-up. A paper appeared describing the strengths and weaknesses of statistical methods that rely on surrogate endpoints, such as CD4 lymphocyte marker levels, in therapeutic trials. The paper emphasizes the need to understand the mechanism of therapeutic action before relying on surrogates. A paper written in collaboration with Dr. Byar of DCPD and many others describes possible strategies for speeding up the evaluation of new treatments without compromising scientific validity.

Other methodologic work includes a published review of methods for evaluating diagnostic tests for cancer, a comprehensive review and bibliography of the use of statistical models in epidemiology in the 1980's (in press), and work on the categorical analysis of measures of agreement when categories are formed by classifying continuous measurements into quantiles, rather than by using predefined levels. A paper with Drs. Gilbert and O'Brien of DCE's Laboratory of Viral Carcinogenesis appeared showing that DNA fingerprints were useful for detecting contamination in tissue cell lines. New statistical techniques were required to account for the fact that one does not know which DNA fragments are associated with particular loci.

One Section member continues to collaborate with members of the Radiation Epidemiology Branch to develop an extensive set of programs for epidemiologic analysis with the IBM-PC. These programs include many special features, such as methods for open cohorts, time-dependent covariates, complex models for the relative hazard, and variance calculations for case-cohort data. Current efforts focus on final testing and editing of a user manual.

Publications:

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04779-15 BB

PERIOD COVERED

October 1, 1990 through September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Field Studies in High Risk Areas

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	W.J. Blot	Chief	BB	NCI
Others:	J.F. Fraumeni, Jr.	Associate Director	E&B	NCI
	R.H. Hoover	Chief	EEB	NCI
	B.J. Stone	Mathematician	BB	NCI

COOPERATING UNITS (if any) Med U SC (S. Schuman); NJ Dpt Hlth (J. Schoenberg); Chin Acad Med Sci (B. Li); Beijing Inst Cancer Res (W. You); Chin Acad Prev Med (S. Yin); Ctr Prev Med (E. Buiatii); USC (S. Preston-Martin); Emory U (R. Greenberg); CA Hlth Dpt (D. Austin); LSU (P. Correa); UCLA (M. Samloff); Rutgers U (C.S. Yang); NHLBI (A. Ershow)

LAB/BRANCH

Biostatistics Branch

SECTION

Analytical Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

7.5

PROFESSIONAL:

6.5

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The objectives of this project are to identify and describe environmental and host determinants of cancer in areas at high risk of cancer through the use of analytical epidemiologic and biometric techniques, particularly case-control studies of specific cancers. A case-control study of renal cancer continued during the year in Minnesota, which leads the nation in rates of this malignancy. The study will evaluate the role of diuretics, widely-prescribed medications recently linked to renal tumors in experimental animals. A parallel international investigation in northern Europe and Australia also was begun. Data analyses from a large multicenter study of oral cancer showed that use of mouthwashes high in alcohol content may increase risk, consistent with the well established increase in risk of these cancers associated with drinking alcoholic beverages. Protective effects were found for diets high in fresh fruit and vegetable intake among both blacks and whites, but somewhat lower levels of consumption may contribute to the high rates of oral cancer among blacks. In studies in high-risk areas overseas, fruit, fresh vegetables, and vitamin C and E intakes were associated with reduced risk of both intestinal and diffuse type stomach cancer in Italy. Dietary patterns help account for the markedly lower risk of this cancer in southern Italian provinces. In China, air pollution from home heating and cooking was found to contribute to the elevated rates of lung cancer in Shenyang, but no effect of indoor radon was detected. Vitamin/mineral intervention trials continued in Linxian, a rural Chinese county with the world's highest rate of esophageal cancer, as did an investigation of the determinants of gastric precancerous lesions and their rates of transition to stomach cancer in Shandong Province.

PROJECT DESCRIPTIONNames, Title, Laboratory and Institute Affiliations of Professional Personnel Engaged on This Project:

W.J. Blot	Chief	BB	NCI
J.F. Fraumeni, Jr.	Associate Director	E&B	NCI
R.H. Hoover	Chief	EEB	NCI
B.J. Stone	Mathematician	BB	NCI
L.A. Brinton	Chief, Environmental Studies Section	EEB	NCI
L.M. Pottern	Epidemiologist	EEB	NCI
L.M. Brown	Epidemiologist	BB	NCI
J.H. Lubin	Health Statistician	BB	NCI
R.G. Ziegler	Cancer Expert	EEB	NCI
M.S. Linet	Cancer Expert	BB	NCI
R.G. Hayes	Cancer Expert	EEB	NCI
J.K. McLaughlin	Epidemiologist	BB	NCI
S. Wacholder	Senior Staff Fellow	BB	NCI
W. Chow	Senior Staff Fellow	BB	NCI
W. You	Visiting Scientist	BB	NCI
S. Yin	Visiting Scientist	BB	NCI
R. Kneller	Staff Fellow	BB	NCI
A. Hsing	Staff Fellow	BB	NCI
M.H. Schiffman	Medical Staff Fellow	EEB	NCI
D.T. Silverman	Epidemiologist	BB	NCI
L. Keefer	Chief, Chemistry Section	LCC	NCI
S. Dawsey	Senior Staff Fellow	DCPC	NCI
P. Greenwald	Director	DCPC	NCI
P.R. Taylor	Epidemiologist	DCPC	NCI

Objectives:

To identify and describe the environmental determinants of cancer in areas where cancer rates are high.

Methods Employed:

Field studies are conducted in areas of the United States and abroad where cancer rates are high and etiologic hypotheses can be tested. The studies are generally case-control investigations whereby cancer patients and controls, or their next-of-kin in the event they have died, are interviewed regarding lifetime histories of residence, occupation, tobacco consumption, diet, and medical or other factors. Comparison of responses between the cases and controls are made by analytical, biometric and epidemiologic techniques to identify, estimate, and evaluate cancer risk factors. When a particular suspect environmental or occupational exposure among a well-defined population group is recognized, cohort investigations may be initiated to determine the group's cancer experience.

Often both the case-control interview and the cohort studies are preceded by reviews of cancer incidence and mortality data and appropriate death certificates and medical records for cancer cases and controls for comparisons of available information. Occasionally, randomized experimental trials may be initiated to test the effectiveness of suspected protective agents in the high risk areas.

Major Findings:

Collaborative case-control and cohort studies in the United States: This year analyses of data from the largest investigation of oral and pharyngeal cancer, a case-control study involving nearly 1,200 cancer patients in Atlanta, New Jersey, Los Angeles, and the San Francisco area revealed significant protective effects associated with vitamin supplement use, particularly vitamins E and A. Low education was found not to be an independent risk factor for oral cancer (after adjustment for tobacco and alcohol), but a low percentage of years worked was. Additional analyses found that users of mouthwash experience an increased risk of this cancer. The excess was only for mouthwashes high in alcohol content, suggesting that topical exposure to alcohol may increase the risk of this cancer. Follow-up of the oral cancer patients continued during the year in attempts to ascertain the risks of second primary cancers and their causes.

Data are being analyzed from case-control studies of biliary tract cancer and renal pelvis and ureter cancers conducted in collaboration with the University of Southern California, New Jersey Department of Health and the University of Iowa. Cigarette smoking has been found to account for almost 3 out of 4 of the cancers of the renal pelvis and ureter. Examination of the role of analgesics in the etiology of these tumors is also a prime focus. Cigarette smoking has been linked to biliary tract cancers in a preliminary analysis.

A large-scale, population-based study of renal cell cancer was initiated last year to follow-up on leads identified in recent studies, including one by NCI, implicating diuretics as a major risk factor. Over 600 patients with renal cancer in Minnesota, which leads the nation in incidence of this cancer are being enrolled. Results from the study should be available before the end of 1992.

International studies: A major emphasis is the conduct of analytical biometric/epidemiologic studies in areas of the world that offer special opportunities for research on cancer etiology. The Branch is collaborating with governmental institutions in case-control, cohort, and intervention studies in China, Japan, Italy, Sweden, Denmark, West Germany and Australia.

In Linxian, which has one of the world's highest rates of esophageal cancer, two large-scale randomized intervention trials drew near completion during the year. One trial focuses on 3,400 persons with esophageal dysplasia. The other involves 30,000 villagers from the general high-risk population. Participants have been randomly assigned to one of several groups to receive different combinations of vitamins and minerals or placebo over a 6-year period. A two-group design (multivitamin vs. placebo) is being used for the dysplasia trial. A more complicated eight-group design, based on a one-half replicate of a 2⁴ factorial design, is used for the general population trial. The studies, now in their sixth and fifth years, respectively, will evaluate whether certain groups of

vitamins and minerals can inhibit late-stage progression to cancer in a high-risk population with multiple micronutrient deficiencies.

In Shenyang and Harbin in northeast China, cigarette smoking was a strong risk factor for lung cancer, with a higher prevalence of smoking among females, compared to elsewhere in China, contributing to the area's high rates. Air pollution was also a significant factor, with risk rising in proportion to exposure to indoor pollutants from coal-burning Kang and other home-heating devices. No link to home radon was found, despite the use of year-long alpha-track radon detectors (the best monitors currently available) and the stability and large size of the population studied.

In an area of Shandong Province, China, with exceptionally high stomach cancer rates, precancerous gastric lesions (i.e., chronic atrophic gastritis, dysplasia) are being evaluated. Three thousand adults in this high-risk area were enrolled in a screening program to detect early cancers and to compare questionnaire items and biochemical markers between groups with various precursor lesions. Initial results suggest that atrophic gastritis is nearly universal among adults, but dysplasia affects males about twice as often as females.

Three occupational cohort studies in high-risk areas of China drew near completion during the year. Follow-up of approximately 100,000 workers exposed to benzene should enable the most precise estimation yet available of the benzene-leukemia dose-response relation, plus an evaluation of whether benzene induced other cancers. In a follow-up of 16,000 persons with silicosis in five provinces in central China, plus 54,000 persons heavily exposed to silica without silicosis, initial analyses suggest a relationship between silica exposure and lung cancer, although some inconsistencies exist. Follow-up of nearly 30,000 tin miners and smelter workers in Yunnan province, where lung cancer rates are exceptionally high, is assessing interactions between these carcinogens and examining time-related factors in cancer induction.

In Italy, analyses of data continued from a case-control study of stomach cancer, in collaboration with the Center for the Study and Prevention of Cancer in Florence and with other institutions. This year, for both intestinal and diffuse type stomach cancer, increased risks were associated with certain traditional soups and meats, while decreased risks were linked to intake of fresh fruits and vegetables, including garlic consumption, and of vitamins C and E. Analyses underway are seeking to detect the presence of oncogenes in tissue from patients with familial history of stomach cancer, and to evaluate correlations in risk with infection with *H. pylori*.

A multicenter study of renal cancer was launched in Sweden, West Germany, Denmark and Australia to evaluate diuretic and other drug use as well as a variety of environmental and host factors for this cancer which occurs at high rates in these areas. The methods parallel those of the investigation in Minnesota so that data can later be pooled.

Publications:

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01CP05498-06 BB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Consulting on Epidemiologic Methods

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	M.H. Gail	Head, Epidemiologic Methods Section	BB	NCI
Others:	T.R. Fears	Mathematical Statistician	BB	NCI
	R.J. Carroll	Visiting Statistician	BB	NCI
	J.G. Benichou	Epidemiol. & Biostat. Training Fellow	BB	NCI
	J.H. Lubin	Health Statistician	BB	NCI
	P.S. Rosenberg	Staff Fellow	BB	NCI
	S. Wacholder	Senior Staff Fellow	BB	NCI

COOPERATING UNITS (if any) Hemophilic Study Group; Mothers & Infants Cohort Study Group; U. of Cal. at Berkeley (W. Winkelstein); Cancer Inst. of the Chinese Acad. of Med. Sci. (J.Y. Li); Veterans Admin. Clinical Trials Program; NIAID (S. Vermund, L. Schragger); U. Tübingen, Germany (A. Krämer, K. Dietz); McGill U., Canada (J.F. Boivin); NCHS (J. Massey); NYU Medical Ctr. (M. Marmor); U. of Pittsburgh (J.J. Mulvihill)

LAB/BRANCH

Biostatistics Branch

SECTION

Epidemiologic Methods Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

3.3

PROFESSIONAL:

2.9

OTHER:

0.4

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Major efforts included: (1) obtaining additional data on the extent of treatment for HIV infection and its impact on AIDS incidence trends; (2) publishing estimates of the numbers infected with HIV in the United States obtained by backcalculation; (3) projecting the incidence of AIDS-related non-Hodgkin's lymphoma through 1992; (4) assisting members of the Viral Epidemiology Section on the design, conduct, and analysis of studies of the natural history of HIV infection and of biological markers; (5) studying dose and time relationships between radiation exposure and the development of thyroid cancer and benign thyroid nodules; (6) studying the risks of lung cancer induced by radon exposure in uranium mines and in the home environment; (7) studying the effects of combined exposure to radon, arsenic and smoking in a case-control and cohort study of lung cancer in China; (8) examining dietary and smoking associations with risk of prostate cancer and stomach cancer; (9) studying possible effects of fluoridation on cancer risks, including the risk of osteosarcoma; (10) collaborating on cohort and case-control studies of the epidemiology of cervical intra-epithelial neoplasia and its relation to human papillomavirus; (11) studying long term mortality trends of persons treated for childhood cancer; (12) studying the association between thoracic radiation for Hodgkin's disease and elevated risk of coronary artery disease; and (13) providing statistical consultation and advice on the use of newly developed computing packages for epidemiologic analysis.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

M.H. Gail	Head, Epidemiologic Methods Section	BB	NCI
T.R. Fears	Mathematical Statistician	BB	NCI
J.H. Lubin	Health Statistician	BB	NCI
S. Wacholder	Senior Staff Fellow	BB	NCI
P.S. Rosenberg	Staff Fellow	BB	NCI
J.G. Benichou	Epidemiol. & Biostat. Training Fellow	BB	NCI
D.P. Byar	Chief, Biometry Branch	DCPC	NCI
J.J. Goedert	AIDS Coordinator	EEB	NCI
W.A. Blattner	Chief, Viral Epidemiology Section	EEB	NCI
J.M. Byrne	Visiting Associate	CEB	NCI
J.D. Boice	Chief, Radiation Epidemiology Branch	REB	NCI
E. Ron	Senior Staff Fellow	REB	NCI
P.R. Taylor	Chief, Cancer Prevention Studies Branch	DCPC	NCI
R. Biggar	International AIDS Coordinator	EEB	NCI
D.T. Silverman	Epidemiologist	BB	NCI
A. Hsing	Epidemiology Fellow	BB	NCI
M. Schiffman	Epidemiologist	BB	NCI
R. Kneller	Epidemiologist	BB	NCI
M.A. Tucker	Head, Family Studies Section	EEB	NCI
R. Hoover	Chief, Environ. Epidemiol. Branch	EEB	NCI
D. Caussy	Fogarty Fellow	EEB	NCI
J.F. Fraumeni	Associate Director	EBP	NCI
S.S. Devesa	Epidemiologist	BB	NCI
R. Yarchoan	Senior Investigator, Clinical Oncology Program	DCT	NCI
J. Pluda	Senior Investigator, Clinical Oncology Program	DCT	NCI
S. Broder	Director, National Cancer Institute		NCI

Objectives:

To promote the use of sound methodology in a wide range of observational and experimental studies by collaboration or consultation and to examine ongoing studies in order to find areas that require new methodological research. Section members may offer extensive support for the experimental design, data management, and analysis of selected studies.

Methods Employed:

Standard and innovative biostatistical and epidemiological procedures are used, as required.

Major Findings:

Dr. Lubin, in collaboration with members of the Radiation Epidemiology Branch and extramural researchers, is preparing a parallel analysis of six cohorts to develop more precise estimates of radiation risk for thyroid cancer and benign thyroid nodules and to study patterns of risk by gender, time since exposure and age at

exposure. A related manuscript, written in collaboration with Dr. M.A. Tucker of the Family Studies Section and others, defines the effects on the thyroid of high dose radiation in children, and found no diminution of risk at very high doses, contrary to theoretical expectations. In collaboration with Dr. S. Akiba of the Radiation Effects Research Foundation and others, Dr. Lubin examined the effects of radiation exposure in survivors of the atomic bomb attacks in Hiroshima and Nagasaki and found that the relative risk of thyroid cancer could be modelled as linear in radiation dose with an excess relative risk of 0.011 per cGy.

Dr. Lubin is also planning parallel analyses of studies of radon exposure, both among uranium and other hard rock miners and among persons exposed in the home environment. Some of this research on radon will be in collaboration with staff at the Department of Energy and the National Council of Radiation Protection and Measurement. A related paper with Dr. J.M. Samet (University of New Mexico) showed that uranium miners exposed to lower radon levels than in previous studies had lung cancer risks in line with extrapolations from previous studies. Dr. Lubin is preparing data files from a large case-control study in Gejiu, China and from a cohort of 19,000 members of the Yunnan Tin Corporation to examine the joint risks from exposure to radon, arsenic and tobacco products and to better define the effects of rate of exposure, duration of exposure, and age at first exposure. A subset of the case-control data will provide detailed cumulative exposure assessments based on non-invasive bone measurements of Pb^{210} levels.

Several staff members have collaborated on studies of dietary exposures and smoking. Dr. Lubin and other Branch staff are preparing an analysis of about 460 cases of lung cancer from Yunnan, China and 1,000 controls to determine associations with intake of fruit and vegetables and to examine the role of smoking, water pipes, and other exposures to tobacco. Dr. Wacholder, in collaboration with other Branch staff, published a report showing increased risks of prostate and stomach cancer among smokers in a cohort of 17,633 male insurees. In collaboration with Dr. Hoover of the Environmental Epidemiology Branch (EEB) and others, Dr. Lubin found no elevation in cancer risks in general for persons exposed to fluoridated water (Report to the Director of NCI) and no elevation in risk for osteosarcoma, which had been implicated weakly in animal studies.

Dr. Wacholder is collaborating with other Branch staff and with Dr. Schiffman of the Environmental Studies Section of the Environmental Epidemiology Branch (EEB) on a cohort study to relate the incidence of non-invasive cervical intra-epithelial neoplasia to the presence of various strains of human papillomavirus (HPV). A related case-control study in Taiwan will examine the relationships between HPV and cervical dysplasia in an unscreened population with more advanced disease. Dr. Wacholder collaborated with Branch staff and members of EEB's Occupational Studies Section to design a nested case-control study in China to examine dose-response relationships between benzene exposure and several hematologic abnormalities, including leukemia.

Dr. Fears has been working with Dr. J. Byrne of the Clinical Genetics Section, Clinical Epidemiology Branch, to evaluate the long term consequences of treatment for childhood cancer. A manuscript has been submitted describing the increased risk of menopause in the age range 21-30 years among those treated for childhood cancer. Recent work shows that excess mortality rates persist in the age range 21-30,

especially for those treated in their late teens with radiation and alkylating agent chemotherapy. A published letter confirms a more favorable survival experience for women than men who survive childhood cancer. Dr. Lubin, in collaboration with Dr. J.-F. Boivin of McGill University, found that radiotherapy treatment of Hodgkin's disease was associated with a 1.8-fold increase in the risk of coronary artery disease over an average follow-up period of seven years.

Staff in the Epidemiologic Methods Section are supporting efforts of the Viral Epidemiology Section (VES) to study the natural history of AIDS. Dr. Gail is collaborating in a cohort study of mothers and infants at risk of developing AIDS. A manuscript is in press indicating that exposure to HIV in utero has no significant effects on measurements made at birth, such as Apgar score and birth weight. Dr. Fears has collaborated with Dr. Caussy of VES in an analysis to determine whether the prognostic significance of disease markers depends on the age of the patient. Drs. Gail and Rosenberg worked with Dr. Krämer of Tübingen University to study the prognostic utility of the joint use of helper lymphocytes, neopterin and β_2 -microglobulin.

Dr. Rosenberg, in collaboration with Dr. Gail and members of the VES, published a manuscript that gave estimates based on backcalculation of the numbers of persons infected with HIV in the United States through 1985 and through mid-1987. The paper discusses uncertainties in these estimates, and provides separate estimates by race, gender, and exposure group. Similar calculations are in progress for Germany, in collaboration with Klaus Dietz of the Tübingen University and for Dallas, Texas, where the results from backcalculation will be compared with seroprevalence estimates from survey samples. This latter effort is being done in collaboration with Dr. J. Massey of the National Center for Health Statistics.

Dr. Rosenberg led a collaborative effort to relate the extent of treatment use in various subgroups of HIV infected individuals to current AIDS incidence trends. This publication extends earlier work that showed that treatment can account for much of the recent favorable change in AIDS incidence rates among homosexual men and provides valuable data on access to treatment in various subgroups. Collaborators who provided information on extent of treatment were at the National Institute of Allergy and Infectious Diseases, the Burroughs-Wellcome Company, the University of California at Berkeley, and New York University Medical Center.

Drs. Rosenberg, Gail and Carroll developed backcalculation methods that incorporate treatment effects and changes in the surveillance definition of AIDS in order to project AIDS incidence in the United States in the 1990s. This material was presented at a special invited workshop at the Centers for Disease Control. Results from the workshop will be used in making official Public Health Service projections.

Dr. Gail served as Chairman of the Operations Committee that monitored the progress of a placebo-controlled clinical trial of azidothymidine, sponsored by the Veterans' Administration, among patients with AIDS-related complex. Dr. Gail and his colleagues were asked to advise staff at the Centers for Disease Control on the implications of treatment on the AIDS epidemic. Dr. Gail, in collaboration with staff from VES; the Clinical Oncology Branch, DCT; the Division of Cancer Prevention and Control (DCPC); and the NCI Director, projected the incidence of AIDS-related non-Hodgkin's lymphoma (NHL). One method based on extrapolation of SEER incidence

trends was in agreement with models that utilized projected AIDS incidence and new information on the risk of developing NHL following the diagnosis of AIDS. These models indicate that between 8% and 27% of all NHL cases incident in 1992 will be AIDS-related.

Dr. Gail, in collaboration with members of DCPC, wrote a manuscript on the design of a large-scale randomized study of interventions to reduce smoking. Eleven matched pairs of cities were selected, and one member of each pair has been randomly allocated to active intervention while the other city serves as control.

Dr. Gail is collaborating with Dr. Blot and with members of DCPC to monitor a large-scale randomized trial to determine whether vitamin supplements can reduce gastric and esophageal cancer incidence. The treatment codes will be unmasked and treatment comparisons made in the coming year (see also Z01CP04779-14 BB).

Dr. Benichou is collaborating with Drs. Gail and J. Mulvihill (University of Pittsburgh) to derive realistic assessments of uncertainty for individualized estimates of breast cancer risk. He is also collaborating with other Branch staff to apply newly developed statistical methods for attributable risk to a case-control study of bladder cancer.

Dr. Fears participated in a conference sponsored by the Committee on Toxicology of the U.S. National Research Council to consider carcinogenic mixtures and the epidemiologic implications of combined exposures.

Staff members also provided numerous consultations on statistical methodology and computer methods during the year. In particular, Dr. Lubin has given numerous consultations to assist members of the Program in the use of a powerful set of computer programs for epidemiology called EPITOME, which Dr. Lubin helped develop.

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ANNUAL REPORT OF
THE CLINICAL EPIDEMIOLOGY BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1990 through September 30, 1991

The Clinical Epidemiology Branch plans and conducts independent and collaborative studies on the distribution and determinants of human cancer, with special emphasis on host factors as detected by clinical observations, and on epidemiologic and laboratory research for clues to carcinogenic mechanisms. Other studies concern cancer in relation to exposures to ionizing radiation or certain viruses; the health and reproductive performance of persons who were treated successfully for childhood cancer; the use of national mortality data developed within the Branch to describe geographic and other demographic features or to test hypotheses about cancer deaths; the development of new epidemiologic resources; and the provision of overviews, consultations and advice, when requested, at the local, national and international level.

STAFFING

John J. Mulvihill, M.D., Head of the Clinical Genetics Section, retired from the Public Health Service on May 16, 1990, to become the Founding Chairman of the Department of Human Genetics at the University of Pittsburgh. Dilys M. Parry, Ph.D., became the Acting Head of the Section. On June 30, 1991, Frederick P. Li, M.D., Head of the Clinical Studies Section based in Boston, retired from the Public Health Service to become Professor of Clinical Epidemiology at the Harvard School of Public Health and at the Dana-Farber Cancer Institute. Both he and Dr. Mulvihill developed their careers from scratch, beginning as Postdoctoral Fellows in the Branch 20-24 years ago. We have recruited an excellent pediatric-oncologist, H. Stacy Nicholson, M.D., of the Children's National Medical Center (CNMC), whose special interest is late effects of childhood cancer and its treatment.

OFFICE OF THE CHIEF

Radiation Effects

Chernobyl: At the end of September 1989, Dr. Miller and Dr. Beebe were members of a group to consult in Kiev on the health effects of the Chernobyl accident. Sponsorship was by the Department of Energy and the Nuclear Regulatory Commission. The Clinical Epidemiology Branch set three objectives: 1) to hold a workshop on the detection of thyroid dysfunction, 2) to hold another on leukemia, and 3) to develop protocols as a solid foundation for population-based studies. Dr. Beebe and Dr. Wachholz of the Radiation Effects Branch, NCI, organized the thyroid workshop, which was held in the Ukraine in conjunction with a World Health Organization (WHO) meeting on the same subject in December 1990. Future collaboration in studies of thyroid disorders is somewhat clouded by changing research personnel in Kiev, uncertainty about the quality of the data collected thus far, and the Soviets' perceived need to examine the total exposed population rather than sampling. Dr. Beebe and Dr. Wachholz expect to revisit Minsk and Kiev in June 1991 to determine

what more can be done with regard to thyroid studies, taking into account a protocol under consideration by the US-USSR thyroid group for Chernobyl. Dr. Beebe and Dr. Stuart C. Finch of the Robert Wood Johnson Medical University in Camden, NJ, visited Minsk and Kiev in October 1990 to evaluate the opportunity for studying leukemia. A U.S. workshop on the subject was held in Bethesda in April 1991 and included participants from the Pediatric Branch, NCI.

Radiation Effects Research Foundation (RERF): A senior medical student from the University of Buffalo spent a month on elective with us. Because she had trained and worked as a biostatistician for five years before entering medical school, and because there is a need to educate replacements for the three experts on intrauterine effects of radiation who are approaching retirement, we asked her to reevaluate data from the survivors of in utero exposure to the atomic bombs in Japan, and Marshalllese children exposed to fallout from a nuclear weapons test on Bikini in March 1954. From these well-worked data of the past she developed four new graphs that substantially clarify understanding of these effects. One shows no severe mental retardation when exposures were under 0.61 Gy (61 rad). This finding, contrary to popular belief, is evidence of a threshold effect. Another new graph, which concerns adult cancers among those exposed during gestation, shows peculiarities that argue against an excess that is due to radiation exposure. Brief reports of these findings are being prepared for publication.

Dr. Miller visited the Radiation Effects Research Foundation (RERF) from April 30-May 3, 1991, to discuss research there in relation to its contract with the Radiation Epidemiology Branch (REB), NCI. A report prepared for REB described the new sense of mission at RERF because, under the leadership of its Director, Itsuzo Shigematsu, M.D., it has become a center for advice and training of Soviets responsible for follow-up studies after Chernobyl, and for the WHO and International Atomic Energy Agency (Vienna) with regard to their radiation studies in the USSR. Also, studies of cytogenetics and molecular biology have been greatly strengthened by the growth of Dr. Akiyama, Chief of Laboratory, in this area. His recruitment of a promising young staff, and a strong link with Lawrence-Livermore Laboratories through the Chairman of the Science Council of RERF. Activities under the NCI contract should move in the direction of molecular epidemiology.

A prototype pilot study, begun by Dr. Beebe and others several years ago, was published. It concerned the feasibility of investigating individual variation in cell-killing in vitro by acute radiation exposures of fibroblasts from A-bomb survivors with and without breast cancer at several radiation dose-levels. No relationship was found. The same study is now being conducted by REB staff with respect to germ line mutations of the p53 gene.

In collaboration with the REB and the RERF, Dr. Beebe is embarking on a study of liver cancer among A-bomb survivors. A detailed protocol was prepared during the year. The results should be helpful in clarifying the difference between high LET radiation from alpha particles (e.g., Thorotrast exposure) and low LET radiation from the A-bomb in the induction of liver cancer. The study may lead to another on the relationship between radiation exposure and hepatitis B infection in liver carcinogenesis.

52-Year Follow-up After an Intrauterine Radiation Overdose: As verified by hospital records, a 52-year-old man had been exposed in the 30th week of gestation to radium-implant therapy given to his mother for cancer of the uterine cervix. The estimated dose to his head (vertex presentation) was 180-300 cGy. A comprehensive history and

medical examination revealed no cancer, cataracts, cytogenetic abnormalities, impairment of cerebral function or fertility. He had three children, a master's degree in social work and a pilot's license. A report has been submitted for publication.

Advice and Consultation: Dr. Beebe is a key contributor to the Committee on Interagency Radiation and Policy Coordination in preparing a consensus statement on risk estimates as based on the 1990 BEIR V Report issued by the National Academy of Sciences coupled with the corresponding 1988 Report of the U.N. Scientific Committee on the Effects of Atomic Radiation. He is also contributing to the Interagency Committee's deliberations on the planning for research in the event of a nuclear power plant accident in the U.S.

Bone Cancer Etiology

Preparation of a chapter on the epidemiology of bone cancer, using data from the Surveillance, Epidemiology and End Results (SEER) Program, showed that not only is Ewing's sarcoma rare among blacks (as was first reported by the Branch in 1969), but also there was an absence of chordoma among blacks, as compared with about ten cases expected. Chordoma arises from vestiges of the notochord, an embryonic structure. Why more than one type of bone cancer is rare in blacks requires further attention.

The literature review also revealed 25 cases of diverse bone cancers and a few soft-tissue sarcomas at the site of metal implants for hip replacement or repair of fractures. Among the neoplasms were seven osteosarcomas, six malignant fibrous histiocytomas and two Ewing's sarcomas. The effect has also been found in experimental animals, and chromium, the most constant component of the alloys used, is a known human carcinogen. A separate report on this finding is being prepared for publication.

Non-Hodgkin's Lymphoma (NHL) Cluster

Dr. Miller chaired a three-person consultative group at the University of Rochester where there is great concern because five employees in one building (average daily census of 150 employees) developed NHL between 1984 and 1989. Every conceivable environmental agent had been measured by the University, and no elevated levels were found. The consultants asked that NCI review pathology specimens for each tumor and that case records be made available to NCI to seek personal or family histories of immunosuppression.

Hepatitis B Infection and Liver Cancer

Dr. Beebe's studies of hepatocellular carcinoma (HCC) among about 50,000 veterans who, in 1942, were given yellow fever vaccine contaminated with hepatitis B virus, are nearing completion. He and James Norman, Ph.D., of the National Heart, Lung and Blood Institute, have been summing up a series of studies that include new information from a case-control study on data from veterans hospitals to determine if, among those with HCC, vaccination against yellow fever in 1942 was more frequent than in the comparison groups.

Fluoride

For a year, Dr. Miller served as the Chairman of a Working Group on the Health Benefits of Fluoride for a Report to the Assistant Secretary for Health. The report was needed to put into perspective the finding by the National Toxicology Program that four male rats given water daily containing 79 ppm of fluoride developed osteosarcoma. No comparable effect was found in the human (fluoridation involves 1 ppm of fluoride), and the benefits in preventing dental decay are still substantial.

Development of Epidemiologic Data Resources

An NCI Working Group on Epidemiologic Data Resources was established in 1978 with Dr. Beebe as Chairman. Its purpose is to develop new resources and protect existing ones. Liaison is maintained with important databases under the National Center for Health Statistics (NCHS), the Social Security Administration (SSA), Health Care Finance Administration and the Internal Revenue Service (IRS). Files are tested for their utility.

Efforts have centered on creating a national database on occupation-related mortality. 1) Financial and other support have been provided for a program organized by NCHS and the National Institute for Occupational Safety and Health for state coding of occupation and industry based on death-certificate information. 2) Pilot studies have been made of Continuous Work History samples maintained by SSA, and with the Statistics of Income sample of the IRS. In 1988 the mortality tracing service by SSA, a valuable resource for follow-up studies, was discontinued. An exemption is being sought for its use by other agencies of government. SSA's use of data from IRS W-2 forms has been ruled an illegal disclosure of tax information. Efforts to develop legislation to broaden access to the IRS address list for epidemiologic follow-up studies have been unsuccessful thus far.

U.S.-Japan Activities

Two workshops were held during the year. One was on transgenerational carcinogenesis; i.e., a forebear is irradiated or exposed to chemicals before conception of the offspring, and cancers occur in generation after generation. The effect has been observed experimentally in four countries, and a substantial number of studies show that human exposure of the father before conception of the child is associated with a small increased risk of cancer. There has been no biological basis for such an effect, which defies conventional genetics. The laboratory scientists present argued that the new concept of genomic imprinting could explain the effect, and the conventional geneticists present were unable to shake this proposal. If true, it would still be a mystery as to why cancer rather than birth defects is induced by preconceptional exposure.

The other workshop concerned the origins of renal cell cancer and Wilms' tumor, a high point of which was a report by Prince Masahito of the discovery of Wilms' tumor in eels grown in overcrowded aquaculture. The Branch has participated in advances made in understanding the origins of Wilms' tumor in the human (at least three genes may individually induce this neoplasm). An environmental cause of the tumor in eels may add to the information about etiology, as in trout with liver cancer from aflatoxin.

As a Lecturer sponsored by the Foundation for the Promotion of Cancer Research in Japan, Dr. Miller spoke at the National Cancer Center in Tokyo, Kyushu University, and the Radiation Effects Research Foundation in "Hiroshima on Clinical Clues to Cancer Etiology: How Valuable Have They Been"? The presentations brought up to date some of the observations made by the Branch over the past 30 years.

Pediatric Practitioner Research Award

As a member of the Council on Pediatric Research of the American Academy of Pediatrics, Dr. Miller proposed an award for outstanding office-based research by a pediatrician. The award, now in its sixth year, has revealed some remarkable accomplishments, and has become highly regarded.

CLINICAL STUDIES SECTION

p53 Germ line Mutations in Li-Fraumeni Syndrome (LFS)

Twenty-one years after LFS was first described by the Branch clinically and epidemiologically, the p53 tumor suppressor gene was found to be involved in the inheritance of diverse cancers seen in the syndrome. The six most frequent are breast carcinoma, brain tumors, soft-tissue sarcoma, leukemia, osteosarcoma and adrenal cortical carcinoma. About a year ago, Frederick P. Li, M.D., Head of our Clinical Studies Section in Boston, and Stephen Friend, M.D., of the Massachusetts General Hospital reasoned that the p53 suppressor gene, known to be mutated late in the occurrence of several common cancers, might, as a germ line mutation, be involved in the familial aggregation of certain cancers early in life. DNA was extracted from lymphocytes and fibroblasts of affected family members, and the conserved regions of the gene were sequenced. All five families with the syndrome that were studied showed heterozygous p53 germ line point mutations, and the two cancers that were available for study showed homozygous mutations in the tumor cells. This finding, which furthered understanding of the key role played by the p53 gene in a variety of human cancers, was quickly confirmed in a sixth family studied by other investigators.

Wilms' Tumor Genes

In 1964 the Branch reported that aniridia was associated with Wilms' tumor, due, it was later learned by others, to a deletion of the short arm of chromosome 11. The gene was located at 11p13. The Branch defined the cancers associated with congenital hemihypertrophy, which is often found in Beckwith-Wiedemann syndrome. The gene for Wilms' tumor in this syndrome was located at 11p15.4. A Boston family in which seven children have developed Wilms' tumor revealed no mutation at either locus on chromosome 11. The gene locus is now being sought on other chromosomes. Unlike retinoblastoma, for which only one gene locus is known, Wilms' tumor has at least three. The most recent finding is that another family in which a father and son have both developed Wilms' tumor has a gene mutation at 11p13, as in cases with aniridia.

Hereditary Renal Cell Carcinoma

In 1979, Dr. Li identified a family in Boston in which ten members developed renal cell carcinoma. Only a limited repertoire of laboratory tests concerning pathogenesis was available then. One of them was cytogenetics, which revealed a translocation between chromosomes 3 and 8, which has since been found in sporadic (non-familial) renal carcinoma cells. In the past year, all five surviving members who had been treated for the cancer developed recurrences. One autopsy and two fresh tumor specimens were obtained for chromosome and molecular genetics studies. They show that the derivative chromosome 8 with the rearranged distal 3p had been entirely deleted. The revised hypothesis is that two genes are involved: one at the breakpoint for t(3;8) and the other on distal chromosome 3p. Recent allelotyping by others suggests the presence of two renal carcinoma suppressor genes on chromosome 3. The translocation breakpoint in the family might mark the locus of one of these genes. An attempt is now being made to clone the breakpoint.

Late Effects in Survivors of Childhood Cancer

In 1974, the Branch initiated global interest in late effects among survivors of childhood cancer through a publication on the health of the progeny of their offspring. Many studies along these lines have since been made by other investigators. We are now testing for germ line mutations of p53 among children with cancer who develop second primary tumors well into adult life. Our previous study at the Dana-Farber Cancer Institute revealed 23 such cancers as compared with only two expected. In addition, follow-up study is being made of second primary cancers among survivors of retinoblastoma. An excess is being found only among those with the hereditary form of the disease--perhaps 50 times above expectation.

CLINICAL GENETICS SECTION

A long-term goal of the Clinical Genetics Section is to identify genetic determinants of human cancer. To accomplish this, we conduct interdisciplinary studies of cancer families and genetic disorders that predispose to neoplasia. Clinical evaluations are made of patients with cancer or with preneoplastic syndromes and key first-degree relatives to confirm diagnoses and to seek findings that may have etiologic relevance. DNA from members of these families is then assayed for polymorphic markers, and linkage analyses are conducted to try to map the relevant genes.

Neurofibromatosis Type 2 (NF2)

Mechanisms: Current studies are designed to elucidate clinical and genetic aspects of NF2. This autosomal dominant disorder is characterized by bilateral acoustic neuromas (actually schwannomas of the vestibular nerve) which usually cause hearing loss and vestibular symptoms between the ages of 15 and 40 years. Other common features include other tumors of the brain and spinal cord (especially meningiomas), peripheral and spinal nerve root neurofibromas, and opacities or cataracts of the posterior capsule of the lens. The lens findings were first confirmed by a study done on our patients.

Our study population includes 45 NF2 patients: 29 from 10 multigeneration families and 16 who likely have NF2 as a result of a spontaneous mutation. We have also evaluated 49 first-degree relatives of our patients and 7 unrelated individuals with apparently sporadic unilateral acoustic neuroma.

Associated Ocular Findings: We have now examined the lenses of 40 NF2 patients. This doubles the number of patients examined in our initial study. Posterior capsular lens opacities (PC) have been documented in 21/26 patients (81%) who were from multigeneration NF2 families and in 13/14 examined sporadic patients. This finding now makes it essential to use a careful slit-lamp examination of the lens through a dilated pupil to evaluate individuals with or at risk of NF2. This year, we also identified two other ocular abnormalities in our patients: another lens finding (cortical wedge opacities) in 9 patients; and a very unusual retinal finding (retinal gliosis) in 4 patients from one family. We hope to be able to demonstrate through study of additional patients that these are also pleiotropic effects of the NF2 gene.

Risk Groups for NF2: Because NF2 is an autosomal dominant disorder, first-degree relatives of NF2 patients have a 50% risk for this condition and should be evaluated for any of its manifestations (Risk Group 1). Four other groups of patients are also considered to be at high risk for NF2: youths or young adults with mild cutaneous findings of neurofibromatosis but not NF2 (Risk Group 2); people under age 40 with unilateral acoustic neuroma (Risk Group 3); children or youths with meningioma or schwannoma (Risk Group 4); and people with multiple nervous system tumors not explained by any other disorder (Risk Group 5). Among our patients, most were evaluated for NF2 because they had a positive family history (Risk Group 1). Fourteen patients did not have a family history of NF2; hence, they likely represent new mutations. Most of them (9) fell into Risk Group 2; all had neurofibromas but they did not fit the diagnostic criteria for NF1. In addition, three had cataracts at young ages. Early cataracts were also present in 2 patients with meningiomas and peripheral nerve schwannomas prior to the diagnosis of NF2 (Risk Group 4). Our results suggest that, in the absence of a positive family history, NF2 should be considered in young people without NF1 who have some cutaneous neurofibromas or CNS tumors and cataracts. This information is important for early diagnosis, improved medical surveillance and timely intervention.

Clinical Heterogeneity: We have observed marked interfamily differences in the clinical expression of NF2. In 11 affected members of a family with mild NF2 (characterized by bilateral acoustic neuromas and lens opacities) the average age at diagnosis was 38.3 years. Only 2 had other central nervous system tumors which in both were solitary meningiomas. In contrast, in a family with severe NF2 the average age at diagnosis of the presenting tumors (not always acoustic neuromas) in 13 individuals was 20.6 years. Most had widespread meningiomatosis of the brain and spinal cord and two had optic nerve sheath meningiomas. The average age at death in 10 was 28.4 years. In seven other families, the average age at diagnosis of NF2 fell between these extremes.

Gene Mapping Studies: Gene mapping studies in our families suggest that the NF2 gene is on chromosome 22, but we do not have enough information to confirm this linkage assignment.

We will continue to accrue additional NF2 families and pursue linkage studies in them using highly polymorphic chromosome 22 DNA markers. If chromosome 22 linkage is confirmed, DNA from sporadic individuals (with DNA from their unaffected parents

serving as controls) will be studied for changes in the size of DNA fragments from the region predicted to be near the NF2 gene to help localize the gene further. Both groups will continue to be evaluated clinically to determine predictors of mild versus severe disease and pleiotropic manifestations of the NF2 gene.

NIH Interinstitute Medical Genetics Program

Referred patients are examined to determine the extent of any pre-existing condition or birth defects and for clues to the etiology of cancer in themselves or family members. When exceptional clinical observations are made, appropriate follow-up epidemiologic and laboratory investigations are conducted. For research studies, specified categories of patients are examined and tested according to an established protocol to ensure uniform data collection. Physicians and medical students in training undertake patient interviews, physical examinations, and treatment and counseling under the direct supervision of an attending physician. In the past year the following patients were seen by members of the Branch:

Neurofibromatosis type 2	48
Neurofibromatosis type 1	7
Unilateral sporadic acoustic neuroma	2
Unilateral acoustic neuroma and familial meningioma	2
Precocious puberty: rule-out NF1	1
Familial myofibromatosis	1
Total	61

Morbidity and Mortality in Childhood Cancer Survivors and their Offspring

Over the past 30 years, survival after childhood cancer has increased over 100 percent. Five-year relative survival went from about 28% in 1963 to 67% in the period 1981-1986. This success had been accomplished by increased use of radiotherapy and chemotherapy, agents that have known carcinogenic, teratogenic and mutagenic properties. This project focuses on the late complications of therapy for cancer in childhood or adolescence. Mortality and morbidity, and in particular, second cancers and fertility of long-term survivors of childhood and adolescent cancer, are studied for information on the carcinogenicity, gonadal toxicity, and possible mutagenicity of cancer treatment, to uncover hereditary patterns of cancer, and to delineate the factors that predispose to second cancers.

With regard to second cancers, men and women who had tumors of the central nervous system as children or adolescents were not more likely to develop second cancers than were controls to develop a first cancer. However, they were 14 times more likely to die during the follow-up period than controls; most deaths were directly due to the first cancer, its treatment, or a recurrence.

After diagnosis and treatment for tumors of the bone, survivors (average age = 32 years) were more likely than children with other cancers to develop a second malignancy. Four percent of osteosarcoma survivors had died, while 17 percent of Ewing's sarcoma survivors had died. Three of 28 children given radiotherapy for Ewing's sarcoma developed osteosarcoma at the same site, and two of 82 children with osteosarcoma developed cancers of the type found in Li-Fraumeni syndrome, breast cancer in one and brain tumor and fibrosarcoma in the other.

We found that menopause occurred earlier in cancer survivors, especially after treatment with radiation below the diaphragm and alkylating agents. In fact, by age 32, 50 percent of women treated in this manner would have reached menopause.

We reported that smoking rates were only slightly lower in survivors than in controls, although there was a trend for less smoking among survivors diagnosed more recently.

These studies have been expanded into new areas. Plans are underway to recontact the remaining survivors of our cohort of long-term survivors of childhood cancer to evaluate their risk of second cancers and health problems, and to expand our studies of cancer and birth defects in the offspring of survivors. New areas will include collection of blood specimens for studies of cancer susceptibility. We will collaborate with the Children's National Medical Center to do imaging studies of women treated for Wilms tumor in order to determine the prevalence of uterine anomalies. These and other studies should increase our understanding of long-term complications of childhood cancer, and provide impetus for new clinical trials of less toxic regimens for cancer treatment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

201CP04377-20 CEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Familial, Congenital, and Genetic Factors in Malignancy

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: D.M. Parry Acting Chief, Clinical Genetics CEB NCI
Section

Others: P. Madigan Health Statistician CEB NCI
F.P. Li Chief, Clinical Studies Section CEB NCI
S. Holmes Epidemiology Research CEB NCI
Assistant

COOPERATING UNITS (if any)

Neurogenetics Unit, NINDS (R. Eldridge); Ophthalmic Genetics Branch, NEI (M. Kaiser); Audiology Clinic, NIDCD (A. Pikus)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

2.0

PROFESSIONAL:

1.0

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

To identify genetic determinants of human cancer, cancer families and genetic disorders predisposing to neoplasia are studied in an interdisciplinary approach to gain insights into human carcinogenesis. Study of 40 patients with neurofibromatosis 2 (NF2) confirmed that posterior subcapsular lens opacities (cataracts) are a frequent and early feature of the disorder. Evaluation of the clinical or genetic findings present in 23 of our patients prior to NF2 diagnosis suggested that this disorder should be considered in young people who do not meet the diagnostic criteria for neurofibromatosis 1 (NF1) but have cutaneous neurofibromas or central nervous system tumors and cataracts at a young age. Of course all first degree relatives of affected individuals should also be evaluated for NF2. We have observed marked interfamilial differences in the clinical expression of NF2 based on average age at diagnosis and at death. The three groups comprise one family with mild NF2 (bilateral acoustic neuromas), one family with severe NF2 (extensive meningiomas of brain and spinal cord) and seven families with moderate NF2 (bilateral acoustic neuromas plus meningiomas). Linkage analysis in our NF2 families with chromosome 22 DNA markers is continuing. From comparisons of ratios of head circumference to height in normal individuals, persons with the Nevroid Basal Cell Carcinoma syndrome and persons with NF1, we concluded that NF1 is a true macrocephaly syndrome. Finally, specimens were obtained from 33 families with a variety of different cancer diagnoses that are components of the Li-Fraumeni syndrome for evaluation by PCR of DNA from the p53 gene.

Project DescriptionNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged in this Project:

D.M. Parry	Acting Chief, Clinical Genetics Section	CEB	NCI
P. Madigan	Health Statistician	CEB	NCI
F.P. Li	Chief, Clinical Studies	CEB	NCI
S. Holmes	Epidemiology Research Assistant	CEB	NCI

Objectives:

To identify genetic factors and disorders associated with human cancer and to promote similar studies worldwide. To document patterns of familial aggregation of neoplasms; to study selected disorders and families by genetic and laboratory investigations in an effort to map preneoplastic disease genes and to elucidate carcinogenic mechanisms and the degree to which heredity and the common familial environment contribute to the etiology of neoplasms. To distribute biological specimens from selected subjects to laboratory investigators for etiologic studies by biochemical, cytogenetic, immunologic, viral, and tissue culture methods. To study, similarly, patients with birth defects and other heritable disorders that may predispose to malignancy.

Methods Employed:

Clinical evaluation of patients with cancer or with preneoplastic syndromes and of key first-degree relatives to seek findings that may have etiologic relevance; interviews of patients with cancer or other diseases to ascertain familial occurrences of cancer and birth defects, as well as prior medical and environmental history; documentation of history by reviewing appropriate vital and medical records; collection and distribution of biological specimens from such families. Establishment and maintenance of laboratory collaboration by contract and other means. Invited lectures, reviews, and committee memberships provide ways for stimulating research in cancer genetics.

Major Findings:

The major focus of this project during the last year has been on the neurofibromatoses.

- A. Neurofibromatosis 2 (NF2). The Section has continued its involvement in studies designed to elucidate clinical and genetic aspects of NF2 an autosomal dominant disorder that is characterized by bilateral acoustic neuromas which usually cause hearing loss and vestibular symptoms between the ages of 15 and 40 years. Other common features include other tumors of the brain and spinal cord (especially meningiomas), peripheral and spinal nerve root neurofibromas and opacities or cataracts of the posterior capsule of the lens. The lens findings were first confirmed by a study done on our patients. Our study population

includes 45 NF2 patients: 29 from 10 multigeneration NF2 families and 16 who likely have NF2 as a result of a spontaneous mutation. We have also evaluated 49 first degree relatives.

1. We have now evaluated the lenses of 40 NF2 patients. This is a doubling of the number of patients examined in our initial study. Posterior capsular lens opacities have been documented in 21/26 patients (81%) who were from multigeneration families and in 13/14 examined sporadic patients. When considering the diagnosis of NF2, this finding now makes it essential to use a careful slit-lamp examination of the lens through a dilated pupil to evaluate known, suspected, or at-risk individuals for this potentially early associated manifestation. In addition we have identified two other ocular abnormalities in our patients. Another lens finding, unilateral cortical wedge opacities, has been identified in 9 patients, in two of whom they were congenital. A very unusual retinal finding (retinal gliosis) has been seen in four patients from one family. All four had exotropia in childhood and have decreased vision in the affected eye because the retinal defect involves the optic nerve. This and a similar retinal lesion (retinal hamartoma) have only been reported in 3 other sporadic NF2 patients.
2. Since NF2 is an autosomal disorder, first degree relatives of NF2 patients have a 50% risk for this condition and should be evaluated for any of its manifestations (Risk Group 1). Four other groups of patients are also considered to be at high risk for NF2: youths or young adults with mild cutaneous findings of neurofibromatosis but not NF2 (Risk Group 2); people under age 40 with unilateral acoustic neuroma (Risk Group 3); children or youths with meningioma or schwannoma (Risk Group 4) and people with multiple nervous system tumors not explained by any other disorder (Risk Group 5). We attempted to assess the utility of these risk groups in identifying patients in whom the diagnosis of NF2 should be considered. To do this, we examined the medical records available on 23 of our patients for findings noted before the diagnosis of NF2 was made. On the basis of these findings, we then assigned the patients to one of the 5 risk groups. Nine patients were evaluated for NF2 because they had a positive family history (Risk Group 1). The 14 patients in Risk Groups 2-5 did not have a family history of NF2: hence, they likely represent new mutations. Most of them (9 patients) fell into Risk Group 2: they had a mild cutaneous finding of neurofibromatosis (especially neurofibromas) but they did not fit the diagnostic criteria for NF1. In addition, three had cataracts at young ages. Cataracts were also present in early childhood in 2 patients who had meningiomas and peripheral nerve schwannomas prior to the diagnosis of NF2 (Risk Group 4). Our results confirm the utility of awareness of the risk groups and suggest that the diagnosis of NF2 should be considered, especially in young people without NF1 who have some cutaneous neurofibromas or CNS tumors and cataracts as well as in first degree relatives of affected individuals. These results were presented in a poster session at the annual meeting of the American Society of Human Genetics.
3. We have observed marked interfamilial differences in the clinical expression of NF2. In 11 members of a family with mild NF2 (characterized by bilateral acoustic neuromas and lens opacities) the average age at diagnosis was 38.3

years. Only 2/11 had other central nervous system tumors which in both were solitary meningiomas. In contrast, in a family with severe NF2 the average age at diagnosis of the presenting tumors (not always acoustic neuromas) in 13 individuals was 20.6 years. Most had widespread meningiomatosis of the brain and spinal cord and two had optic nerve sheath meningiomas. The average age at death in 10 was 28.4 years. In seven other families, the average age at diagnosis of NF2 of 26.5 years fell between these extremes.

4. Gene mapping studies in our families suggest that the NF2 gene is on chromosome 22, but we do not have enough information to confirm this linkage assignment. We will continue linkage studies in our families using highly polymorphic chromosome 22 DNA markers.
- B. Neurofibromatosis 1. Our studies of NF1 (von Recklinghausen's disease) continue at a low level. Together with staff from the Family Studies Section, Environmental Epidemiology Branch, we evaluated the relationship between head circumference (HC) and height in normal adults and in patients with either the nevoid basal cell carcinoma syndrome (NBCC) or NF1. Macrocephaly is a feature of many human malformation syndromes (including NF2 and NBCC) in which increased stature may also be a feature. To determine if a large HC is a primary feature of a syndrome or normal relative to height, we determined the correlation between head circumference and height in normal adults and then compared these values with those for the patients. The results suggested that head size appears to be related to proband status in NBCC (e.g., persons with NBCC who have large heads are more likely to be probands (the first member of the family to be diagnosed) but that NF1 is a true macrocephaly syndrome (e.g., individuals with NF1 have large head size regardless of whether or not they were the proband). Objective detection of relative abnormalities in head size may aid in syndrome delineation and diagnosis.

Other Studies. Specimens from individuals with cancer from 33 families which have a predisposition to some of the tumors in the Li-Fraumeni syndrome were identified from an extensive review of our Family Studies Records System and the specimens list from our tissue repository. These were sent to Boston for PCR analysis of the p53 gene.

Scholarly Synthesis. Dr. Parry presented results of gene mapping studies in NF1 and NF2 in a Clinical Center Conference on neurofibromatoses which were published this year as an update for clinicians. She also was an invited speaker at a symposium on NF2 sponsored by the National Neurofibromatosis Foundation. She and her NF2 collaborators prepared a review article for a textbook in neurology on the differential diagnosis of NF2 and the important management considerations. Presentations were made at the annual meeting of the American Society of Human Genetics and at a conference on the "Genetics of Hearing Impairment," sponsored by the New York Academy of Sciences.

Resources. Four contracts continued to provide nationally recognized laboratory expertise for assays of protein and DNA polymorphisms for linkage analysis and for cytogenetic studies of solid tumors. A contract for research support services is also in place. (See contract narratives below).

Publications:

Bale SJ, Amos CI, Parry DM, and Bale AE. The relationship between head circumference and height in normal adults and in the nevoid basal cell carcinoma syndrome (NBCC) and neurofibromatosis 1 (NF1). *Am J Med Genet* (In Press).

Eldridge R, Martuza RL, Parry DM. Neurofibromatosis 2. In: Johnson R, ed. *Current therapy in neurologic disease-3*. Philadelphia: B.C. Decker, 1990;101-8.

Kramers PGN, Gentile JM, Gryseels BJAM, Jordan P, Katz N, Mott KE, Mulvihill JJ, Seed JL, Froberg H. A case study in the feasibility of mutation epidemiology, including a review of the genotoxicity and carcinogenicity of antischistosomal drugs. In: Mendelson ML, ed. *Proceedings of the fifth international conference on environmental mutagens*. New York: Alan R Liss (In Press).

Mulvihill JJ. Introduction and history. In: Korf BR, Rubenstein A, Yahr F, eds. *Neurofibromatosis: a handbook for patients, families and health care professionals*. New York: National Neurofibromatosis Foundation (In Press).

Mulvihill JJ. Lung cancer. In: King RA, Rotter JI, Motulsky AG, eds. *The genetic basis of common disease*. New York: Oxford University Press (In Press).

Mulvihill JJ, Parry DM, Sherman JL, Pikus A, Kaiser-Kupfer MI, Eldridge R. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis): an update. *Ann Intern Med* 1990;113:39-52.

Parry DM, Kaiser-Kupfer MI, Sherman JL, Pikus A, Eldridge R. Neurofibromatosis 2 (bilateral or central neurofibromatosis), a treatable cause of deafness: recommendations for screening and follow-up based on study of one large kindred. In: Rubin RJ, Van de Water T, Steel K, eds. *Genetics of hearing impairment*. Ann NY Acad Sci (In press).

Wertz DC, Fletcher JC, Mulvihill JJ. Medical geneticists confront ethical dilemmas: cross-cultural comparisons among 18 nations. *Am J Hum Genet* 1990;46:377-82.

CONTRACTS IN SUPPORT OF THIS PROJECT

HEALTH RESEARCH INC., ROSWELL PARK MEMORIAL INSTITUTE (N01-CP-71018)

Title: Genetic Factors in Persons at High Risk of Cancer: Solid Tumor Chromosome Analysis

Current Annual Level: \$45,633

Person Years: 0.8

Objectives: To analyze cancer cells and lymphocytes of cancer patients for non-random chromosome abnormalities that may localize oncogenes and tumor suppressor genes.

Major Contributions: In a stromal sarcoma of the uterus, a novel rearrangement involving insertion of an entire chromosome 19 into chromosome 10 has been identified. In the family with renal carcinoma and a constitutional 3;8 translocation, fresh tumor specimens from 2 affected members have revealed loss of the derivative chromosome 8 carrying the distal 3p. In addition, work under this contract has identified non-random chromosome changes in renal carcinomas. The breakpoint in 7 tumors was in 3p. The second most common abnormality was rearrangement of chromosome 5. Also, chromosome 3p arrangements were observed in mesothelioma. Follow-up studies of a radiation resistant patient show that his fibroblast lines were aneuploid and that radioresistance might be an in vitro artifact.

MEMORIAL SLOAN-KETTERING HOSPITAL FOR CANCER AND ALLIED DISEASES (N01-CP-71126)

Title: Genetic Factors in Persons at High Risk of Cancer: Solid Tumor Chromosome Analysis

Current Annual Level: \$58,444

Person Years: 1.0

Objectives: To determine if tumors from persons with cancer have cytogenetic abnormalities which may ultimately be important in tumor etiology.

Major Contributions:

Each of these laboratories (Health Research Inc. and Memorial Sloan-Kettering) have been sent 18 tumor specimens and blood from cancer-prone cases in the last year. Tumor types for which multiple specimens have been submitted include soft tissue sarcoma, osteosarcoma, renal cancer, and mesothelioma. In a patient with osteogenic sarcoma and a history of the familial breast cancer-sarcoma syndrome, a 13q14 deletion was detected in the bone tumor. This is the first familial sarcoma we have successfully karyotyped. In addition, a new case of a t(12;16) in a liposarcoma has been identified, and several new cases of synovial sarcoma with t(X;18) have been

found. In situ hybridization now localizes the breakpoint on the X chromosome as being distal to the OAT locus.

REGENTS OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES (N01-CP-71081)

Title: Genetic Factors in Patients at High Risk of Cancer--Genetic Markers for Linkage Analysis (Assay A--Assays of Protein Polymorphisms).

Current Annual Level: \$56,355

Person Years: .35

Objectives: To provide red blood cell, serum and plasma typings for a panel of 30 polymorphic genetic markers for use in genetic linkage studies.

Major Contributions: The laboratory has received and processed blood and serum specimens from 282 individuals in 15 families representing eight different hereditary disorders. The results of these studies have contributed to the mapping of the genes for multiple endocrine neoplasia type 1, hypertrophic cardiomyopathy and hereditary cutaneous malignant melanoma.

INTEGRATED GENETICS, INC. (N01-CP-71127)

Title: Genetic Factors in Patients at High Risk of Cancer--Genetic Markers for Linkage Analysis (Assay B--Assays of DNA Polymorphisms).

Current Annual Level: \$378,122

Person Years: 4.1

Objectives: To provide DNA polymorphism typings on samples submitted for use in genetic linkage studies.

Major Contributions: The lab has thus far performed a total of 1485 assays on 135 persons from one large and six small families with the multiple endocrine neoplasia type 1 (MEN1) syndrome. The information from this study has contributed to the mapping of the gene for MEN1. An additional 40 DNAs from other members of these seven families plus a new family have been submitted to the laboratory for analysis with chromosome 11 probes. Thirty-five samples from several variant MEN1 families followed by CEB investigators have been sent to the laboratory for analysis with several chromosome 11 markers. Finally, 67 samples from several families with basal cell nevus syndrome were submitted for analysis with the probe C11P11. This work is in progress.

DEPARTMENT OF ENERGY, BROOKHAVEN NATIONAL LABORATORY (Y01-CP-20518)

Title: In Vitro Radiosensitivity and DNA Repair in Genetic Syndromes and Families at High Risk of Malignancy

Current Annual Level: \$310,950

Person Years: 3.2

Objectives: To determine if persons with increased susceptibility to cancer, e.g., members of cancer families, individuals with multiple primary tumors, radiogenic tumors or genetic disorders predisposing to cancer, have abnormal repair of DNA damage induced by UV light, X-irradiation or a variety of chemicals, and when repair defects are found, to identify the underlying cellular mechanisms.

Major Contributions: Coded fibroblast strains sent to the laboratory in the past year have been from Israeli immigrants irradiated in childhood for ringworm of the scalp. The strains consist of two groups: those from persons who developed cancer (usually of the thyroid or skin) following radiation exposure, and those from persons who did not. These strains have been the major focus of the laboratory's recent work.

In order to evaluate possible differences in response to ionizing radiation of the Israeli strains, the laboratory has been trying to develop a method that will distinguish among the cell growth characteristics of strains from normal individuals, persons homozygous for ataxia-telangiectasia (AT), and persons who are heterozygous for AT. This is necessary because we have postulated that the Israelis who developed tumors as a result of the radiation exposure may, in fact, be AT heterozygotes (the AT gene is known to be present in high frequency in the North African population from which the Israeli immigrants came) and possibly have an increased predisposition to radiogenic malignancies as a result. AT is an autosomal recessive condition which predisposes to lymphoproliferative malignancies and, both in vivo and in vitro, has abnormal sensitivity to ionizing radiation. In vitro, the D_{10} values for ionizing radiation of AT homozygotes are significantly lower than for controls, so that the two groups can be distinguished. Although some scientists have reported that the D_{10} values of strains from AT heterozygotes are intermediate between those of the AT homozygotes and normal individuals, this has not been generally confirmed.

To date, the Brookhaven Laboratory has used a variety of different methods to see if any will consistently differentiate AT heterozygotes from normal individuals: these have included x-ray treatment of exponentially growing cells, x-ray treatment of confluent cell cultures, treatment of cell cultures with chronic doses of x-rays and treatment with neocarzinostatin, a radiomimetic chemical. Although none of these approaches can consistently distinguish AT heterozygotes from normal individuals, the laboratory has made parallel studies with the Israeli strains, in case some differences appear among them.

Recently, we broke the strain codes on data sent to us from Brookhaven from all of the studied Israeli strains. Comparison between strains from patients with thyroid cancer and the appropriate controls and from those with skin cancer and their controls showed no statistically significant differences in cell survival characteristics.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01CP04400-26 CEB
PERIOD COVERED October 1, 1990 to September 30, 1991		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Clinical Epidemiology of Cancer		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
P.I.:	F.P. Li	Chief, Clinical Studies Section CEB NCI
Others:	R.W. Miller	Chief CEB NCI
	D.M. Parry	Geneticist CEB NCI
	A.E. Kantor	Expert CEB NCI
COOPERATING UNITS (if any) None		
LAB/BRANCH Clinical Epidemiology Branch		
SECTION Clinical Studies Section		
INSTITUTE AND LOCATION NCI, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.3	1.0
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input checked="" type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input checked="" type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) <p> We study persons who have an exceptionally high risk of cancer to find explanations for their susceptibility. These unusual individuals are identified through referral by practitioners and by our own clinical observations at the bedside. With informed consent, epidemiologic inquiries are made to identify predisposing host and environmental factors, and to quantify the risk of cancer development. Results show that carriers of cancer genes develop cancer at high rates in specific tissues, including multiple primary cancers in childhood. Concurrent laboratory studies are made to clarify biologic mechanisms of cancer susceptibility. In the dominantly inherited syndrome of breast cancer, sarcomas and other childhood neoplasms (Li-Fraumeni family cancer syndrome), the inherited cancer susceptibility was shown to be due to the p53 gene. All 5 families with Li-Fraumeni syndrome that were examined had a germ line point mutation in the p53 gene. Work is in progress to map several other tumor suppressor genes, including genes for renal carcinomas and familial Wilms' tumor. In another study, nearly 1000 patients are under surveillance for the occurrence of second cancers through the Registry of Survivors of Childhood Cancer in Boston. An additional series of 1600 survivors of childhood retinoblastoma in New York and Boston have shown that the subgroup with hereditary retinoblastoma have a 50-fold increase in risk of second cancers, particularly sarcomas, brain tumors and melanoma. </p>		

Project DescriptionNames, Titles, Laboratory and Institute Affiliations of Professional Personnel on this Project:

F.P. Li	Chief, Clinical Studies Section	CEB	NCI
R.W. Miller	Chief	CEB	NCI
D.M. Parry	Geneticist	CEB	NCI
A.E. Kantor	Expert	CEB	NCI

Objectives:

To employ clinical observation at the bedside to find causes of human cancers. Susceptibility factors in the development of cancer are identified and laboratory studies, particularly molecular analyses of oncogenes and tumor suppressor genes, are made to uncover biologic mechanisms of predisposition to cancer. In addition, survivors of childhood cancer are followed for clues to the origins of their cancers that may only emerge in later life.

Methods Employed:

Patients referred for consultation or admitted at the Dana-Farber Cancer Institute are evaluated for clues to the etiology of their neoplasms. When exceptional clinical observations are made, appropriate follow-up epidemiologic and laboratory investigations are conducted. In recent years, several striking family aggregates of specific cancers have been identified. Members of these kindreds are under study to identify reasons for their susceptibility, and to detect early cancers. Prospective studies are in progress to confirm predictions of high risk of cancers in individuals, families, and other groups. Collaboration has been established with basic scientists at NCI and elsewhere to conduct studies of chromosome and molecular changes in tumor cells of mesotheliomas, sarcomas, and renal cancers. In addition, registries have been established of more than 1000 patients who have survived childhood cancer at Dana-Farber Cancer Institute, and 1600 retinoblastoma patients treated in New York and Boston. These patients are being studied to determine the probability of development of a new cancer, and the somatic and genetic effects of the neoplasm in childhood.

Major Findings:p53 Mutations in Li-Fraumeni Syndrome

After a 2 decade search, the p53 tumor suppressor gene was found to be the site of the inherited defect in the Li-Fraumeni syndrome. The disorder features an autosomal dominant pattern of cancers, particularly sarcomas of bone and soft tissue, acute leukemia, brain tumor, adrenocortical carcinoma and breast cancer. Past efforts to find the gene that increases susceptibility to these diverse cancers were unrevealing. In collaboration with Dr. Stephen Friend, Massachusetts General Hospital, we decided a year ago to select the most likely gene, given the range of cancer phenotypes. The p53 tumor suppressor gene seemed a likely candidate. DNA was extracted from lymphocytes and fibroblasts of affected family members, and the conserved regions of the gene were sequenced. All 5 families with Li-Fraumeni

syndrome that were examined showed germ line point mutations in the p53 gene. In one family, the mutation co-segregated with cancer in 4 relatives. In available tumor specimens of family members, the second non-mutant p53 allele was deleted in their cancer cells, as expected in recessive tumor suppressor genes. Our report of p53 mutations in these 5 families was quickly confirmed in a sixth NCI family with the syndrome.

Hereditary Renal Cell Carcinoma

Follow-up studies have been made of a family with 10 cases of renal cancer and a translocation between chromosomes 3 and 8. Studies by us and several other groups have shown chromosome 3p rearrangements in nearly all renal cancer tissues of non-familial cases, suggesting its importance to the development of this neoplasm. In the past year, all 5 surviving cases of renal carcinoma in our t(3;8) family have developed recurrent disease. Fresh tumor tissue was obtained from 2 of them and autopsy specimens from a third. Chromosome and molecular genetics studies show, unexpectedly, that the derivative 8 chromosome with the rearranged distal 3p has been deleted. At present, our hypothesis is that one gene on 3p that is involved in the development of human renal carcinoma is at the breakpoint of the t(3;8) in our family, and that a second critical gene is on distal chromosome 3p. The model is consistent with recent allelotyping data that suggest the presence of 2 renal cancer suppressor genes on 3p. The translocation breakpoint in our family might pinpoint the locus of one of these genes. The work is in progress to clone the translocation breakpoint.

Mapping the Gene(s) for Familial Wilms' Tumor

Studies of the association of Wilms' tumor with aniridia or with hemihypertrophy have led to a search for Wilms' tumor genes on the short arm of chromosome 11. The rarity of Wilms' tumor in families have precluded informative linkage analyses. In our previously reported family with Wilms' tumor in 5 children, follow-up observation has revealed 2 additional cases with the neoplasm. Linkage analysis of this and other available families has excluded chromosome 11p as the locus of the "familial Wilms' tumor gene," and a search for its true location has been initiated. However, we have recently identified a father-son with Wilms' tumor in whom a single base pair deletion was detected in the WT-1 gene on 11p13.

Late Effects in Survivors of Childhood Cancer

A number of studies have been undertaken to evaluate adverse effects of late onset among childhood cancer survivors. In a 14-year follow-up of patients previously studied for the occurrence of second cancers at the Dana-Farber Cancer Institute, 23 new cancers were observed when 2 were expected. All but 2 of the second cancers were solid tumors. The tumors usually occurred within the field of radiation therapy. The findings indicate that the high risk of second neoplasms among childhood cancer survivors extends far into adult life. Testing for germ line p53 mutations is in progress in those survivors with multiple cancers.

A recent study reported a 90% risk of second cancers, primarily sarcomas, among nearly 800 survivors of hereditary retinoblastomas. However, the risk estimate may be flawed by a high proportion of cases lost to follow-up. To refine the risk, a

follow-up study of 1600 survivors of retinoblastoma is in progress. Follow-up was successful in 85% of these cases. Excess second cancer was confined to those with bilateral retinoblastoma. In this group, the relative risk of a new cancer is 50-fold above expectation.

Publications:

Li FP. Cancer families and susceptibility to cancer. In: Paci P. ed. Modulating factors in multistage carcinogenesis. New York: Plenum Press (In Press).

Li FP. Epidemiology of cancer in childhood. In: Nathan DG, Oski F, eds. Hematology of infancy and childhood. 4th ed. Philadelphia: WB Saunders (In Press).

Li FP. Epidemiology of chronic leukemias. In: Wiernik PH, Canellos GP, Kyle RA, Schiffer CA, eds. Neoplastic diseases of the blood, vol. 3. New York: Churchill Livingstone (In Press).

Li FP. Familial aggregation of cancer. In: Schottenfeld D, Fraumeni JF, Jr. eds. Cancer epidemiology and prevention. New York: Oxford Press (In Press).

Li FP. Familial cancer syndromes and clusters. In: Haskell CM, ed. Current problems in cancer, vol. 14. Chicago: Year Book Medical Publishers, 1990;77-114.

Li FP. Studies of cancer-prone families. In: Fortner JG, Rhoades JE, eds. Accomplishments in cancer research. Philadelphia: JB Lippincott, 1990;297-302.

Miller RW. Additional observations on high risk of leukemia. In: Gale RP, ed. UCLA symposium on molecular and cellular biology. New York: Wiley-Liss, 1990;29-33.

Miller RW. Teratology: a key to cancer etiology. A memoir. In: Kalter H ed. Issues and reviews in teratology. vol. 2. New York: Plenum Publishing (In Press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05139-12 CEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

NIH Interinstitute Medical Genetics Program: The Genetics Clinic

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: D.M. Parry

Acting Chief, Clinical
Genetics Section

CEB NCI

COOPERATING UNITS (if any)

CC (S. Schlesinger); NEI (M. Kaiser-Kupfer); NIDDK (B. White); NICHD (W. Gahl, J. Sidbury); NINDS (R. Eldridge); NIDCD (A. Pikus)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

0.50

PROFESSIONAL:

0.5

OTHER:

0.0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Genetics Clinic is a collaborative undertaking by researchers from six NIH institutes and the NIH Clinical Center. Consequently, clinic patients constitute a broad spectrum of genetic disease. The patient load during the clinic's 11th year comprised 260 individuals representing some 60 different diagnostic categories. Of these, 61 patients were seen by members of the Clinical Epidemiology Branch (CEB). For our Branch, the Clinic provides a multidisciplinary setting in which to study unusual patients who either have cancer or an increased risk of developing benign or malignant tumors. Patients are ascertained through special referrals from outside physicians and inhouse requests for etiologic consultations. With informed consent, the approach to the patient includes detailed physical examination and, where applicable, epidemiologic studies of the environmental and genetic background and laboratory studies to clarify biologic mechanisms of carcinogenesis. Categories include patients with genetic diseases predisposing to malignancy, patients with birth defects and cancer, and any other families with an excessive occurrence of cancer of any type.

Project DescriptionNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

D.M. Parry	Acting Chief, Clinical Genetics Section	CEB NCI
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Objectives:

1. To provide a multidisciplinary setting in which patients with cancer or at high risk of developing cancer can be studied through clinical and laboratory collaboration to identify host or environmental factors for increased cancer risk.
2. To provide counseling for persons at high risk of malignancy and recommend appropriate medical surveillance for the early detection of tumors.
3. To provide training to graduate physicians and medical students in the diagnosis, counseling, and treatment of individuals with, or at risk of, genetic disease, and in the research approach to genetic disease.

Methods Employed:

Referred patients are examined to determine the extent of any pre-existing condition or birth defects and for clues to the etiology of cancer in themselves or family members. When exceptional clinical observations are made, appropriate follow-up epidemiologic and laboratory investigations are conducted. For research studies, specified categories of patients are examined and tested according to an established protocol to ensure uniform data collection. Physicians and medical students in training undertake patient interviews, physical examinations, and treatment and counseling under the direct supervision of an attending physician.

Clinic Patients Seen by Members of the Clinical Epidemiology Branch

Neurofibromatosis type 2	48
Neurofibromatosis type 1	7
Unilateral sporadic acoustic neuroma	2
Unilateral acoustic neuroma and familial meningioma	2
Precocious puberty: rule out NF1	1
Familial myofibromatosis	<u>1</u>
Total	61

Major Findings:

1. Much of our research effort continues to be focused on bilateral acoustic neurofibromatosis, known as NF2. This disorder causes development of schwannomas of the vestibular nerve, usually resulting in bilateral hearing loss in adolescent or early adult life. Surgical removal of these tumors presents formidable difficulties because of the risk of facial and auditory nerve damage. This condition is also associated with a high incidence of meningiomas, gliomas and neurofibromas of the spinal nerve roots. Over the last three years, we have evaluated 45 patients with NF2: 29 from 10 multigeneration families together with 35 first-degree relatives and 16 sporadic cases together with 16 first-degree relatives. In addition to a physical examination, the evaluation includes: magnetic resonance imaging (MRI) of the brain with gadolinium, ophthalmoscopy, audiometry and auditory brainstem-evoked responses. Baseline total spine MRIs are now being done on all affected individuals and electronystagmography is being done on affected individuals who have hearing on at least one side and all at risk individuals. Our major findings are the following:
 - a. The ophthalmic studies have been extended to 40 NF2 patients. Posterior capsular lens opacities have now been seen in 21/26 patients from multigeneration NF2 families and in 13/14 NF2 patients in whom the disease is likely the result of a spontaneous mutation. These lens opacities are clearly a pleiotropic effect of the NF2 gene and can be very useful in the early diagnosis of affected individuals. We have identified another lens opacity (a cortical wedge opacity) in several NF2 patients, in two of whom it was congenital. This may be a second lens abnormality in NF2. Finally, 4 members of one NF2 family have a very rare retinal finding (retinal gliosis) that has been previously described in one NF2 patient. We intend to evaluate other members of this family and then report this observation.
 - b. In our series, females with NF2 are diagnosed, on average, seven years earlier than affected males, regardless of whether the disease is familial or sporadic. This suggests that females have earlier manifestations of NF2 and perhaps more severe disease. In support of this, males tend to have bilateral acoustic neuromas as their only intracranial manifestation of NF2, whereas females frequently have multiple meningiomas as well. In addition, among individuals with only bilateral acoustic neuromas, males are much more likely to retain hearing in the absence of surgery than are females. These observations suggest that a conservative approach to management may be appropriate in many males. We intend to quantify the differences in disease expression between males and females further.
 - c. We have not yet confirmed linkage of the NF2 gene in our families to chromosome 22. However, our mapping studies have identified what may be a recombinant between a locus for NF2 and DNA marker D22S1 on chromosome 22. In the past, this was considered to be the closest marker to NF2. We are now testing our families for linkage to the IL2B marker which is on the distal long arm of chromosome 22. This marker is highly polymorphic and may be very informative in our families.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05146-12 CEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Morbidity in Childhood Cancer Survivors and their Offspring

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	J. Byrne	Sr. Staff Fellow	CEB	NCI
Others:	H.S. Nicholson	Visiting Scientist	CEB	NCI
	R.R. Connelly	Statistician	DCPC	NCI
	M.H. Gail	Chief, Epidemiologic Methods	BB,DCE	NCI
	T.R. Fears	Statistician	BB,DCE	NCI
	S. Devesa	Epidemiologist	BB,DCE	NCI
	L. Kessler	Chief, Analytic Studies Sect.	DCPC	NCI
	C.A. Plotzky	Fellow	POB	NCI

COOPERATING UNITS (if any)

NICHD (J. Mills); Children's National Medical Center (D. Johnson); Children's Cancer Study Group (L. Robison); Burkitt's Tumor Project, Ghana (J. Neequaye)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

2.0

PROFESSIONAL:

1.0

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

This project focuses on the late complications of therapy for cancer in childhood or adolescence. Mortality and morbidity, especially second cancers and fertility of long-term survivors of childhood and adolescent cancer, are studied for information on the carcinogenicity, gonadal toxicity, and possible mutagenicity of cancer treatment, to uncover hereditary patterns of cancer, and to delineate the factors that predispose to second cancers.

Current phases include the field work (interviews) for a study of survival after childhood leukemia, analysis of data collected from interviews with 2300 survivors of childhood and adolescent cancer and 3500 of their siblings as controls to learn about their subsequent health and fertility, and the health of their offspring; and planning for an imaging study of women who were treated for Wilms' tumor. From our large study of long-term cancer survivors, we found that menopause occurred earlier in survivors, especially after treatment with radiation below the diaphragm and alkylating agents. Also, we reported that smoking rates were only slightly less in survivors, although there is a trend for less smoking among survivors diagnosed more recently.

These studies have been expanded into new areas. Plans are underway to recontact the remaining survivors of our cohort of long-term survivors of childhood cancer to evaluate their risk of second cancers and health problems, and to expand our studies of cancer and birth defects in the offspring of survivors. This study will consist of an interview and blood specimens for studies of cancer susceptibility. Plans to include blood specimens from our cohort of leukemia survivors are being developed.

Project DescriptionNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. Byrne	Sr. Staff Fellow	CEB	NCI
H.S. Nicholson	Visiting Scientist	CEB	NCI
R.R. Connelly	Statistician	DCPC	NCI
M.H. Gail	Chief, Epidemiologic Methods	BB,DCE	NCI
T.R. Fears	Statistician	BB,DCE	NCI
S. Devesa	Epidemiologist	BB,DCE	NCI
L. Kessler	Chief, Analytic Studies Section	DCPC	NCI
C.A. Plotsky	Fellow	PB	NCI

Objectives:

To document late effects in cancer survivors with special emphasis on fertility and reproductive outcome in patients who become pregnant after cancer treatment. The goals are to test genetic theories of cancer etiology; to define potential gonadal toxicity of cancer treatment, and to provide needed information for genetic counselling of long-term cancer survivors. The hypothesis being tested is that cancer patients have excessive morbidity due to additional malignancies, or other illnesses and impaired reproductive performance, including an increased frequency of offspring with birth defects or cancer.

Methods Employed and Major Findings:

1. The Five Center Study. Intensive analysis continues on the largest and the oldest cohort of survivors of childhood and adolescent cancer yet assembled. Data have been assembled from five collaborating centers on 2498 individuals who had cancer under age 19 years, survived at least 5 years and reached age 21 years. The 3604 controls, chosen from among the siblings of the survivors, were also studied for subsequent morbidity, mortality, quality of life, fertility and health of offspring. Among the results generated from this study during the past year are the following:

- Survivors of tumors of the central nervous system had significant deficits in many areas of living, including hearing and sight. In each of these areas, men were more likely to do worse than women.
- Adult survivors of childhood bone tumors are at high risk for premature death and second malignancies, especially those who had Ewing's sarcoma. Nonetheless, despite the threat of cancer and physical impairment of amputation, overall quality of life, by the measures used in this study, seemed only mildly affected.
- Menopause occurred earlier in female survivors compared to controls. The chief risk factors were diagnosis after age 12 and treatment with combination radiation below the diaphragm and alkylating agents. Among women treated before age 13 the risk of menopause was not raised. Among women treated after age 12 and who were still

menstruating at age 21 the risk of menopause was greatest during the first 5-year period of follow-up (i.e., ages 21 through 25). Treatment with either radiotherapy or alkylating agents alone significantly increased the relative risk of early menopause during the early 20s (RR= 4 and 9, respectively). Combination therapy with radiation below the diaphragm and alkylating agents greatly increased the risk of early menopause during the early 20s (RR=29), and also during the later 20s (RR=4.64). We estimate that for women treated with combination therapy and who were still menstruating entering their twenties, the median age at menopause was about 32, compared to 49 for control women.

- Despite their high risk for having another cancer, childhood cancer survivors were only 20% less likely to be currently smoking when compared to their matched siblings. However, survivors treated in the most recent time period covered by the study had reduced their smoking to nearly half that of controls.
- Prevalence of cancer survivors in the United States With the Applied Research Branch of the Division of Cancer Prevention and Control, we estimated that 5.7 million adults in the US in 1987 had ever had a non-melanoma skin cancer, about 3.3% of the adult population. Approximately 89,000 adults had cancer during childhood, or 1.6% of the total. These estimates are in good agreement with estimates developed by others.

Other preliminary results:

- There is no evidence that potentially mutagenic cancer therapy is actually linked to an excess of genetic effects in the offspring. Other endpoints (e.g., sex ratio and fetal loss) are being studied.

2. Late Effects after Childhood Leukemia. A collaboration with the Children's Cancer Study Group and the National Institute of Child Health and Human Development is in place to study late effects in leukemia survivors. This interview study deals with the general health and fertility of survivors, including second cancers. Field work is in progress, and analysis will begin in the fall 1991. Approximately 750 leukemia survivors and 600 sibling controls will be interviewed for the study. NICHD has contributed about 40% of the cost of the study.
3. Follow-up of Medulloblastoma Survivors. Through a collaborative arrangement with the Children's National Medical Center (CNMC) in Washington we have followed 35 survivors of medulloblastoma using clinical and neuropsychological evaluations. Survivors' families have been interviewed by telephone, and survivors have been seen for clinical evaluation and neuropsychological testing.
4. Clinical Evaluation of Survivors of Wilms' Tumor. In collaboration with radiologists and oncologists at the Children's National Medical Center, a study is underway to follow-up girls and women who were diagnosed with Wilms' tumor to

determine the frequency of malformations of the uterus. New imaging techniques and a clinical evaluation will determine the etiology of pregnancy wastage including uterine malformations.

5. Follow-up of Women Treated at NIH for Childhood Leukemia. With the Pediatric Oncology Branch of NCI, we are planning a clinical follow-up of 35 women reported originally in 1976 to determine whether the gonadal dysfunction seen then persisted, and to evaluate their menstrual history and current gonadal functioning.
6. Second Evaluation of Survivors from the Five-Center Study. Since the Five-Center Study is the largest and the oldest cohort of survivors yet assembled for the purpose of examining late effects, this cohort will be recontacted over a decade from the first interview, when their average age will be 43 years. The study is now being developed and will focus on second tumors, late morbidity and early deaths in survivors and risk of cancer or birth defects in offspring of survivors. Investigators at the centers have expressed their willingness to collaborate.
7. Follow-up of Survivors of African Burkitt's Lymphoma. Through a contractual arrangement set up by the Viral Epidemiology Section of the Environmental Epidemiology Branch, we are collaborating with Dr. Janet Neequaye of the University of Ghana Medical School to study the fertility of long-term survivors of African Burkitt's lymphoma. Preliminary results indicate that women who survived Burkitt's lymphoma reached menarche on average later than controls. Bloods from Ghana stored at the Frederick Cancer Research and Development Center will be analyzed for altered gonadotropin levels to see if there is any lasting endocrine damage.
8. Prevalence of Cancer Survivors in the United States. Other papers planned include a study of the level of functioning of cancer survivors in the community, and the knowledge survivors have of cancer risk factors. An earlier paper on smoking confirmed that people who survived cancer in childhood had about the same smoking rates as the general population; if this is true for the US population, it may be that cancer survivors are unaware of, or ignore their high risk for another cancer and other late effects, as exhibited by their level of awareness of cancer risk factors.
9. Scholarly Synthesis. Reports on aspects of this project were prepared for journals serving various readerships--oncologists, oncology nurses, pediatric oncologists; as well as books on medical oncology, pediatric oncology, and environmental mutagenesis. Presentations were made at the International Cancer Congress; at the International Symposium on Multidisciplinary Approaches to CNS Tumors in Childhood in Santa Margherita, Italy; and at annual meetings of the Society for Epidemiologic Research, the American Society for Clinical Oncology, and the Irish Society for Social Medicine.

Publications:

Byrne J. Fertility and pregnancy after malignancy. In: Beardsley DC, ed. Semin Perinatol 1990;14:423-9.

Byrne J, Fears TR, Gail MG, Pee D, Connelly RR, Austin DF, Holmes GF, Holmes FF, Latourette HB, Meigs JW, Strong LC, Myers MH, Mulvihill JJ. Early menopause in survivors of childhood cancer. Am J Ob Gyn (In Press).

Byrne J, Fears TR, Nicholson HS. Sexual differences in cancer survival: hormones or stage at diagnosis? [Letter to the Editor]. JAMA 1990;264:1810.

Byrne J, Mulvihill JJ. Long-term survivors of childhood and adolescent cancer: Their fertility and the health of their offspring. In: Plowman PN, McElwain TJ, Meadows AT, eds. The complications of cancer management. Guildford: Butterworth-Heinemann, 1991;114-27.

Mostow EN, Connelly RR, Mulvihill JJ, Byrne J. Quality of life in long-term survivors of central nervous system (CNS) tumors in childhood and adolescence. J Clin Oncol 1991;9:592-9.

Neequaye JE, Byrne J, Levine PH. Menarche and reproduction after treatment for African Burkitt's lymphoma. Br Med J (In Press).

Nicholson HS, Mulvihill JJ, Byrne J. Late effects of therapy in adult survivors of osteosarcoma and Ewing's sarcoma. J Clin Oncol (In Press).

Ursell PC, Byrne J, Strobino BA, Gersony WM. Growth of the great vessels in the normal human fetus and in the fetus with cardiac defects. Circulation (In Press).

Warburton D, Byrne J, Canki N. Chromosome anomalies and prenatal development: an atlas. New York: Oxford University Press, 1991;3-104.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05279-08 CEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Development of Epidemiologic Data Resources

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	G.W. Beebe	Statistician (Health)	CEB	NCI
Others:	M.C.R. Alavanja	Epidemiologist	OAD,EBP	NCI
	A.E. Blair	Epidemiologist	EEB	NCI
	J.D. Boice	Chief	REB,EBP	NCI
	W.J. Blot	Chief	BB	NCI
	B.F. Hankey	Chief	CST,DCPC	NCI
	R.H. Hoover	Chief	EEB	NCI
	Z. Hrubec	Expert	REB,EBP	NCI

COOPERATING UNITS (if any)

None

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

0.4

PROFESSIONAL:

0.3

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

An NCI Working Group on Epidemiologic Data Resources was established in 1978 by the Director, NCI, with Dr. Beebe as chairman. Its charge was to identify and develop new data resources and to protect existing ones. The Working Group has occupied itself with a wide variety of tasks: promotion of computerized record linkage, development of a national database for occupational mortality, obtaining and retaining access to administrative files of Federal agencies, seeking new databases, providing oversight on the use of the hospital discharge database of the Veterans' Administration hospital system, advising the National Center for Health Statistics on its National Death Index, and reviewing all Master Order Agreement-Requests for Proposals. It has also been trying to promote a legislative initiative that would broaden access to the address file of the Internal Revenue Service beyond its present scope that is limited to occupational studies and studies of war veterans.

Project DescriptionNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged in This Project:

G.W. Beebe	Statistician (Health)	CEB	NCI
M.C.R. Alavanja	Epidemiologist	OAD,EBP	NCI
A.E. Blair	Epidemiologist	EEB	NCI
J.D. Boice	Chief	REB,EBP	NCI
W.J. Blot	Chief	BB	NCI
B.F. Hankey	Chief	CST,DCPC	NCI
R.H. Hoover	Chief	EEB	NCI
Z. Hrubec	Expert	REB,EBP	NCI
S.K. Zahm	Epidemiologist	EEB	NCI

Objectives:

1. To develop and facilitate access to data files likely to be useful for epidemiologic research.
2. To encourage the linkage of large administrative data files in the interest of epidemiologic research.
3. To oversee exploitation of the Veterans' Administration hospital discharge file, to advise on draft Requests for Proposals from holders of Master Order Agreements, and to advise on the National Death Index.

Methods Employed:

Liaison is maintained with developers of significant databases, e.g., National Center for Health Statistics (NCHS), Social Security Administration (SSA), Health Care Finance Administration, and Internal Revenue Service (IRS). The potential utility of files is tested through pilot projects. Information is sought on data systems in use elsewhere. Legislative change is sought in the interests of epidemiologic research. Presentations are made in which restrictions on the flow of information are described.

Major Findings:

1. Efforts to create a national database for occupational mortality include provision of financial and other support for state coding of occupation and industry on the death certificate, a program organized by the National Center for Health Statistics and the National Institute for Occupational Safety and Health, pilot work with the Continuous Work History Sample maintained by the Social Security Administration, and pilot work with the Statistics of Income sample of the Internal Revenue Service.

2. The shut-down, in 1988, of the mortality tracing service formerly maintained by the Social Security Administration (SSA) has led to high-level discussions to clarify the SSA position and seek an exception for sister agencies within DHHS. Disclosure of information on living subjects that SSA previously obtained from W-2 forms has been ruled to be an illegal disclosure of tax information, but both SSA and HCFA have independent sources of information on older Americans.

3. Efforts, thus far unsuccessful, continue to develop a legislative initiative to broaden access to the IRS address list for epidemiologic research. An attempt will now be made to include in draft material a provision permitting SSA to disclose the fact that an income tax return was filed in a recent year as evidence that the subject was probably alive at that time.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05280-08 CEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Carcinogenic Effects of Ionizing Radiation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	G.W. Beebe	Statistician (Health)	CEB	NCI
Others:	R.W. Miller	Chief	CEB	NCI
	C.E. Land	Statistician	REB,EBP	NCI
	J.D. Boice	Chief	REB,EBP	NCI
	B.W. Wachholz	Chief	REB,CPCP	NCI

COOPERATING UNITS (if any)

None

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

1.5

PROFESSIONAL:

1.0

OTHER:

0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The program is directed at the synthesis and extension of existing knowledge of the carcinogenic effects of ionizing radiation. The activities of the Branch are coordinated with those of the Radiation Epidemiology Branch and the Radiation Effects Branch. Both Dr. Miller and Dr. Beebe have been extensively involved over the years in the research on the atomic-bomb survivors in Japan and draw heavily on that experience in lectures, consultations, and scientific articles on radiogenic cancer.

Recent foci of interest include variation in individual sensitivity to the carcinogenic action of ionizing radiation, time-response characteristics of radiogenic cancers, the contrast between low- and high-linear energy transfer (LET) radiation with respect to their influence on liver cancer, the likelihood that important new knowledge might come from properly designed studies of the post-Chernobyl experience in the USSR, how to reach a Federal consensus on risk estimates for radiogenic cancer that would serve the needs of the regulatory agencies, consultation with the Radiation Effects Branch, NCI, on the studies of leukemia and thyroid cancer in relation to fallout from the weapons tests in Nevada, and whether it would be prudent to do some advance planning for research that might be carried out following a nuclear power plant disaster in the U.S.

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on This Project:

G.W. Beebe	Statistician (Health)	CEB	NCI
R.W. Miller	Chief	CEB	NCI
C.E. Land	Statistician	REB,EBP	NCI
J.D. Boice	Chief	REB,EBP	NCI
B.W. Wachholz	Chief	REB,CPCP	NCI

Objectives:

1. To evaluate the carcinogenic risk of ionizing radiation in terms of dose parameters, host characteristics, and environmental factors.
2. To determine the limits of knowledge of the carcinogenic effects of ionizing radiation and suggest research to extend that knowledge.
3. To suggest how knowledge of differential risks of cancer from exposure to ionizing radiation may be used in research on carcinogenic mechanisms.

Methods Employed:

The literature on the carcinogenic effects of exposure to ionizing radiation is continuously monitored. Review papers are prepared and needed research suggested. Membership on various research committees provides opportunities for gaining new information, testing the soundness of interpretations, and stimulating investigation.

Major Findings:

1. With investigators from the Radiation Effects Research Foundation and the Brookhaven National Laboratory, pilot work was published demonstrating the feasibility of investigating individual variation in cell-killing by acute radiation exposure of fibroblasts from A-bomb subjects with and without breast cancer and exposed at very different dose levels.
2. With investigators from the Radiation Epidemiology Branch, Brookhaven National Laboratory, and Israel, variation in individual susceptibility to radiogenic thyroid cancer is being studied in relation to heterozygosity for ataxia-telangiectasia (A-T) in children irradiated in Israel for tinea capitis.
3. As the DHHS representative on the Science Panel of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET) Committee on Interagency Radiation Research and Policy Coordination, Dr. Beebe is a member of the sub-panel reviewing the BEIR V report of the National Academy of Sciences and the 1988 report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) with the objective of providing the Federal agencies with a consensus on risk estimates. He also advises the Committee on the scope of research that might fruitfully be undertaken on the basis of a nuclear power plant accident in the U.S.

Other topics currently before the Science Panel are electro-magnetic (EM) radiation health hazard and research needs, research agenda for neutron effects and occupational exposure assessments, and review of radiation protection concepts and recommendations.

4. Together with investigators at the Radiation Effects Research Foundation and the NCI Radiation Epidemiology Branch, a study was begun on liver cancer among the A-bomb survivors. It is hoped that this study will clarify the difference between alpha and gamma irradiation in the induction of liver cancer. It may also set the stage for a study of the respective roles of the hepatitis B virus and ionizing radiation in the incidence of hepatic cell carcinoma.

5. The Clinical Epidemiology Branch and the Radiation Effects Branch are cooperating with the Department of Energy and the Nuclear Regulatory Commission in trying to organize epidemiologic studies of the post-Chernobyl experience in the USSR. Thus far, the emphasis is on thyroid cancer and leukemia. Visits were made to Kiev and Minsk to lay the basis for planning a research protocol for leukemia, and a U.S. leukemia group has been formed to make more specific plans. A visit to Minsk was made to explore the possibility of collaborative work on thyroid cancer, and in December 1990 the U.S. thyroid group attended a World Health Organization symposium on thyroid cancer in Chernigov, Ukraine, followed by a bi-national workshop in Kiev on the development of a formal study of thyroid cancer in the Ukraine. Communication has not been easy or complete, and in April 1991 the U.S. thyroid group met at NIH in an effort to accelerate progress toward a mutually acceptable study design.

Publications:

Ban S, Setlow RB, Bender MA, Ezaki H, Hiraoka T, Yamane M, Nishiki M, Dohi K, Awa AA, Miller RC, Parry DM, Mulvihill JJ, Beebe GW. Radiosensitivity of skin fibroblasts from atomic bomb survivors with and without breast cancer. Cancer Res 1990;50:4050-5.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05329-08 CEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hepatitis B Virus and Liver Cancer in Army Veterans of WW II

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: G.W. Beebe Statistician (Health) CEB NCI

COOPERATING UNITS (if any)

Medical Follow-Up Agency, Institute of Medicine, NAS (J. Norman); Veterans Administration, Six Hospitals (L. Seeff); NIDDKD (J.H. Hoofnagle)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

0.3

PROFESSIONAL:

0.2

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

There are three arms to the study: (1) a serologic survey of representative veterans in three comparison groups; (2) a case-control study of discharges from Veterans Administration hospitals for liver cancer vs. several other major forms of cancer; and (3) a cohort study of mortality based on death certificates and review of available clinical and pathology reports for deaths in the period 1946-1983. The first phase, published in The New England Journal of Medicine in 1987, involved the comparison of laboratory findings in three groups: (1) men hospitalized with acute hepatitis in 1942; (2) men vaccinated from contaminated lots of yellow fever vaccine who did not become ill in 1942; and (3) men who entered the Army after contaminated vaccine had been withdrawn. The second phase foundered on small numbers arising from the inadequacy of diagnostic indexing by Veterans Administration hospitals. The third phase makes use of the mortality in three cohorts of about 20,000 each, defined as in the first phase. Only a single carrier was found in the serologic survey, and the mortality survey provides no evidence to believe that the carrier rate in the critical second group was in any way exceptional. The small excess mortality from primary hepatic cell cancer is inconsistent with expectation based on studies in Taiwan and elsewhere. Overall, the findings suggest that the likelihood of liver cancer following infection with the hepatitis B virus depends on age at infection and is low for healthy young males.

Project DescriptionNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged in This Project:

G.W. Beebe	Statistician (Health)	CEB NCI
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Objectives:

To verify the long-held view that the hepatitis B virus was responsible for the 1942 epidemic; to test, in an area of low incidence for primary hepatocellular cancer (HCC), the hypothesis that infection with the hepatitis B virus (HBV) leads to HCC; to measure the long-term (40 year) persistence of the type B antigen and antibodies; to compare long-term mortality from HCC in men with acute icteric hepatitis following yellow fever vaccination with that in men vaccinated from the same contaminated lots who remained free from clinical disease; to investigate the hypothesis that the pathogenesis of HBV-associated HCC is marked by a prior cirrhotic stage; to determine the prevalence of chronic hepatitis in 40-year survivors of infection with HBV; and to explore host and environmental factors for their possible role in any association between HBV infection and HCC.

Methods Employed:

A principal task preliminary to the conduct of both the serologic survey and the mortality survey was to identify representative men in the three groups defined above. The first group, men acutely ill with icteric hepatitis in 1942, was selected from epidemiologic questionnaires completed in Army hospitals during the 1942 epidemic. The second group, men with subclinical infections (immunized from contaminated lots without becoming ill), was initially identified from payroll rosters of units reporting large numbers of hepatitis cases and then collated with the Army tape file of hospitalizations in 1942 to eliminate those who were hospitalized with hepatic disease, however coded. The validity of this group was confirmed by looking up the individual immunization records of a sufficiently large sample to establish a 95 percent confidence interval of 88 to 98 percent. The third group, men with no exposure to contaminated vaccine, was drawn from tape files of Government life insurance taken out by men entering the Army well after the contaminated vaccine had been withdrawn and replaced by one containing no blood products.

Assays were available that would surely identify individuals with prior hepatitis A or B virus infection and those chronically infected with HBV (for C, no assay was available in 1985 when the project was started). Representative samples of Army veterans in the three groups defined above were bled and tested for serum aminotransferases, HBsAg, anti-HBs, anti-HBc, anti-HAV, HBeAg, HBsAg subtype, DNA-polymerase activity, HBsAg titer, and serum levels of HBV-DNA.

In the case-control arm of the study, Veterans Administration hospital discharges for cancers of the liver, lung, stomach, and colon among WW II Army veterans were matched on relevant variables and compared as to Army records of yellow fever vaccination, including lot number of vaccine. The records for discharges indexed to

liver cancer were reviewed to segregate HCC from metastatic liver cancer and coding errors.

The few available (the 1972 fire having destroyed most records) original Army immunization records were reviewed blind for both cases and controls.

The cohort mortality arm of the study involved mortality ascertainment through the facilities of the Veterans Administration (VA), procuring copies of death certificates, and coding them as to both underlying and associated causes of death. A sample of apparent survivors was submitted to the National Death Index as a check on the completeness of the mortality tracing through the system of the Veterans Administration. Since death certificate diagnoses of liver cancer are known to be unreliable, every effort was made to obtain sufficient information from clinical and pathology records to review the diagnoses of liver cancer on the death certificates. The three groups were then compared as to mortality over time (1946-1983), cause of death, and associated conditions given on the death certificates. They were also compared as to mortality from, specifically, HCC as determined by the diagnostic review.

When it became clear that any excess mortality from HCC among men with subclinical infections was slight, a roster of Army WW II veterans compensated in 1957 for chronic hepatitis was investigated as to mortality from liver cancer and also hospitalization in the VA system with a diagnosis of liver cancer.

Major Findings:

1. The serologic survey (New England Journal of Medicine, 1987) showed that the 1942 epidemic had been caused by HBV and that high titers still persisted 43 years after infection. Only one carrier was identified in 1985 among 392 veterans administered contaminated vaccine, and he was not in the subclinical group.
2. Analysis of mortality in the three large cohorts revealed no excess deaths from non-alcoholic cirrhosis or hepatitis, and only a small and statistically insignificant excess of primary liver cancer as identified from the death certificates. The results of the diagnostic review are more suggestive of excess HCC mortality among the subclinical group. The numbers are small and by no means inconsistent with the hypothesis that HBV infection plays an etiologic role in HCC. They do not, however, suggest that the risk of HCC is especially high among adult males in good general health at the time of infection.
3. The study provides fairly strong evidence that the chronic carrier rate following HBV infection in young adult males is well below the 5-10 percent level that has been generally assumed. The inference drawn from the study is that the relationship between HBV infection and HCC probably depends on age at infection. For adult males infection with HBV seems to be followed by a low carrier rate and perhaps also by a low transition probability from the carrier state to HCC.

Publications:

Beebe GW, Norman JE. Study of the likelihood of hepatocellular carcinoma following the 1942 U.S. Army epidemic of hepatitis B. In: Tabor E, DiBisceglie AM, Purcell RH, eds. Etiology, pathology, and treatment of hepatocellular carcinoma in North America. Houston: Gulf Publishing, 1991;3-13.

ANNUAL REPORT OF
THE ENVIRONMENTAL EPIDEMIOLOGY BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1990 through September 30, 1991

The objective of the Environmental Epidemiology Branch (EEB), is to generate and test ideas concerning the environmental and host determinants of cancer by a broad range of epidemiologic studies based on knowledge and application of clinical medicine and oncology, statistical methodology, new developments in carcinogenesis, and resources best available at the national level.

A number of young scientists joined the Branch within the past year in a variety of fellowship positions. These include Drs. Howard Strickler, Lawrence Figgs, Timothy Coté, Jeffrey Streuwing, and Rashina Sinha. Dr. Walter Stewart from Johns Hopkins University also joined the Occupational Studies Section for one year under an Interagency Personnel Agreement. In addition, three students participated in training opportunities through the Student Research Training Program. The EEB also continues to provide a focus for training of a number of foreign scientists. In the past year, scientists from Italy, Costa Rica, Germany, China, Trinidad, Nigeria, and Sweden spent varied periods of time in the Branch, engaging in collaborative analyses of a number of data sets.

RESEARCH PROGRAM:

The Branch conducts a broad-based research program with respect to exposures assessed, types of cancers evaluated, and specific methods employed. In order to summarize these activities, we often group individual studies into categories which describe integrated research programs focused in particular areas.

Descriptive Studies: To identify, systematically, the geographic variation and clustering of cancer mortality, the Branch has analyzed U.S. cancer mortality on a county level. In the past, cancer death rates were computed and reported along with maps illustrating the variation. These patterns were also related to demographic and potential exposure information at the county level through correlational or hypothesis-generating studies, thus providing a series of etiologic leads that might explain the variations observed.

In the past year, we have investigated lung cancer incidence patterns from 1969 through 1986 by age, race, sex, and histologic type. The patterns were best described by birth cohort, with the rise and fall in squamous cell cancer rates preceding those for small cell and adenocarcinoma by 10 to 20 years within each race-sex group. This histology-specific pattern of rise and fall in rates by birth cohort occurred first for white males followed by black males, followed in turn by white females and then black females. Overall, the rates for squamous cell carcinoma among both sexes and for adenocarcinoma among men were substantially higher for blacks, whereas no racial disparity was seen for small cell carcinoma.

In response to concerns over possible carcinogenicity of fluoride compounds added to drinking water raised by the results of a recent animal experiment, we evaluated 36 years of U.S. cancer mortality and 15 years of cancer incidence data in relation to the fluoridation status of drinking water supplies for the individual counties under study. Osteosarcomas of the bone were singled out for detailed analysis based on the results of the animal experiment. Among both males and females residing in counties having undergone rapid fluoridation, the relative risks of death from cancers of the bones and joints were the same after 25-30 years of fluoridation as was in the years immediately preceding fluoridation. A similar lack of a relationship to timing of fluoridation was noted for the incidence of bone and joint cancers and osteosarcomas. The mortality and incidence data in this ecologic study allowed an evaluation of the patterns of risks for virtually all forms of cancer in relation to the timing of fluoridation of drinking water supplies. No consistent evidence was found for a relationship between any malignancy and pattern of fluoridation. Thus, in a study of over 2.3 million cancer deaths in fluoridated counties across the United States, and over 125,000 incident cancer cases in fluoridated counties covered by two population-based cancer registries, we identified no trends in cancer risks that could be ascribed to the consumption of fluoridated drinking water.

Finally, an updated atlas of maps illustrating cancer mortality trends over three decades among nonwhites was published. This serves as the companion volume to a similar atlas illustrating trends in whites. For most cancer sites, trends in U.S. mortality rates for nonwhites resembled those for whites over the 30 years from 1950 to 1980. However, among tumors with upward trends, the rates rise much faster among nonwhites than whites. For example, the rates of increase among nonwhite males for cancers of the oral cavity, larynx, esophagus and prostate were 20 to 100 times greater than the corresponding trends among white males. Among nonwhite women, breast cancer mortality rates have risen by 1.6% every five years, compared to 0.1% among white women. With respect to geographic variation over time, as noted for whites, the mortality patterns for most sites among nonwhites showed increasing geographic uniformity over time. There were some exceptions to this pattern, the most notable being the emergence in the 1970's of high rates for prostate cancer among black men in the South Atlantic states and rising rates of stomach cancer among native Americans in the Southwest.

Occupational Studies: Epidemiologic studies of occupational groups are valuable, since workers often have heavy and prolonged exposures to suspect carcinogens. Studies of these groups can therefore lead to measures to reduce the risk to workers, and can identify the potential hazard of agents which are also found in the general environment. In addition, detailed studies of groups occupationally exposed to known carcinogens can provide insights into the basic mechanisms of human carcinogenesis. The Branch initiates studies in the occupational area to (a) explain unusual geographic distributions of cancer incidence or mortality, (b) identify high-risk subgroups within broad industrial categories, (c) pursue clues provided by animal bioassays or clinical observations, and (d) assist outside agencies or institutions in evaluating the health experience of workers.

The occupational studies program continues to focus on assessment of agricultural exposures. A study of leukemia among adults in Iowa and Minnesota revealed an excess risk ($RR=1.2$) among farmers, with the greatest risk ($RR=1.4$) seen for chronic lymphocytic leukemia. Risks of over twofold occurred among farmers exposed to several animal insecticides including carbaryl, coumaphos, dichlorvos, fampur, methoxychlor, nicotine, pyrethrins, and toxaphene. Risks associated with the use of insecticides on crops were generally lower, possibly because crop applications occur in less confined spaces, resulting in lower exposures. A study focused on possible biological mechanisms for the association of herbicide exposure and non-Hodgkin's lymphoma was initiated in Iowa. A battery of immunologic assays of farmers before, during, and after periods of heavy herbicide application is planned.

A follow-up study of workers with silicosis identified a 2.6-fold excess risk of lung cancer that was not altered by control for cigarette smoking, and was greater than that seen among either coal miners with pneumoconiosis or among metal miners. This provides substantial support to the belief that silica itself may play an important role in occupational lung cancer risks.

The program of studies focused on assessment of solvents was also continued. No significant excesses of cancer mortality were seen in a cohort of workers exposed to phenol. Provocative deficits of risks were noted for mortality from arteriosclerotic heart disease, emphysema, and cirrhosis of the liver. The risk of these diseases decreased with increasing duration or intensity of exposure to phenol. Although these may be chance findings, the ability of metabolites of phenol to serve as free radical scavengers suggests a biologic mechanism that might generate such results. In a study of workers employed at an aircraft maintenance facility, excesses of multiple myeloma and non-Hodgkin's lymphoma were noted among those exposed to several organic solvents. These risks were particularly prominent for women.

Reanalysis of a case-control study of testicular cancer conducted in the late 1970's and early 1980's revealed a twofold excess risk among men who served in the military in Vietnam. This is particularly provocative since a previous study conducted by the EEB revealed a similar excess risk of testicular cancer among military working dogs who had served in Vietnam. Several efforts are underway to clarify what aspect of the Vietnam experience might be responsible for these excesses.

There was a continued emphasis on methodologic investigations targeted on improving the quality of occupational studies of cancer in general. Recent assessments have included an evaluation of the quality of pesticide exposure histories obtained for farmers from surrogate respondents, a study of the determinants of risks among short-term factory workers, and a study of the sources of variation in exposure to several chemicals on the part of embalmers. Results of the surrogate respondent study indicated that interviews with wives of farmers agreed 80% to 100% on the ever/never use of specific pesticides with information obtained directly from their husbands.

The correspondence for frequency of use was less (60%) but still high enough to conclude that wives are useful sources of such information concerning their husbands' exposures. A study of short-term workers in the formaldehyde industry confirmed the excess risk for several causes of death that has been seen in other studies. However, contrary to a common belief, short-term workers were not assigned to jobs with heavier exposures than those who were to become long-term workers. The study of embalming exposures indicated that ventilation, concentration of embalming fluids, type of case, and spills were the most important factors governing air concentrations of formaldehyde and other chemicals. These data can now be used to develop exposure assessment tools to clarify the reasons for the cancer excesses noted among embalmers.

Medicinal Agents: The Branch conducts a variety of studies to assess drug-induced cancer. Such studies have been valuable in the discovery of previously unrecognized carcinogenic hazards, and they have allowed insights into mechanisms of carcinogenesis. This has been so, not necessarily because of the presence of a large burden of drug-induced cancer in our society, but rather because the exposure usually involves high doses which can be assessed by standard epidemiologic approaches. In conducting this research, staff members monitor epidemiologic, clinical and laboratory observations for candidate drugs that can be evaluated for carcinogenic effects utilizing special resources developed by the Branch. This includes the surveillance of clinical trials for long-term effects, follow-up of specific patient populations, intensive case-control investigations, and record-linkage studies within prepaid health plans. In recent years, the focus of this program has been primarily on hormonal medications and cytotoxic drugs, although a variety of other agents have also been evaluated.

Analyses of cancer incidence in a cohort of Swedish women treated with non-contraceptive estrogens for menopause showed significantly increased risk of endometrial cancer; a slightly decreased risk of cervical cancer; and no difference in the risk of cancers of the ovary, pancreas, large bowel or kidney. The risk of liver or biliary tract cancers was significantly lower than expected, particularly in women who used more potent estrogens, while the risk of breast cancer was slightly elevated overall.

A preliminary analysis of mortality in a cohort of U.S. women revealed a 20% reduction in risk of all-cause mortality associated with the use of menopausal estrogens. The reduction appeared limited to recent users, with no duration-response gradient, and the reduction was not seen among women with higher family incomes, suggesting that selection bias may account for at least part of the overall protection.

In an analysis of risk of invasive cervical cancer in five U.S. centers, risk was reduced among users of barrier contraceptives. However, this appeared to result mainly from the concomitant use of spermicidal agents, which is of note given their proven anti-viral capabilities.

Nutritional Studies: Indirect evidence that diet and nutrition are related to cancer risk is substantial. The Branch continued its activities in this area to test some of the current hypotheses and to generate additional testable hypotheses. Dietary exposures currently being assessed include consumption of specific food groups and food items, such as meat, fruits and vegetables, ethnic dishes, and coffee; macronutrient and micronutrient intake such as fat,

vitamin A, carotenoids, vitamin C, folacin, and trace minerals; general nutritional status; anthropometry; biochemical indices, such as serum cholesterol and serum beta-carotene; and storage and cooking practices. Cancers being studied include those of the colon, rectum, breast, lung, cervix, pancreas, prostate, and oral cavity.

An interdisciplinary study of breast cancer identified a significant relationship between low plasma beta-carotene and breast cancer, while other carotenoids and tocopherols were not associated with the disease after adjustment for other risk factors.

In a study of diet and cervical cancer risk in five U.S. centers, the intake of carotenoids, vitamin A, vitamin C and folate was unrelated to risk of either in situ or invasive disease. This was true even when comparing the extremes of intake of these micronutrient, which spanned a three- to fourfold range. In a serologic analyses of cervical cancer cases and controls from Australia, no differences were found in selenium levels.

In a case-control study of cancers of the vulva, consumption of a variety of micronutrients, including vitamin A, estimated total carotenoids, beta-carotene, vitamin C and folate, were unrelated to risk of disease. However, increases in risk were seen with decreased intake of dark yellow-orange vegetables and alpha-carotene based on one of the first analyses to utilize recently available data on the individual carotenoid content of common fruits and vegetables.

Data collection for three major investigations of cancer sites thought to be related to dietary fat intake (i.e., breast, endometrial and prostate cancers) was completed and all three studies are currently in analysis.

In-depth Studies of Specific Cancers: The Branch conducts studies of selected cancer sites that are not necessarily limited to high-risk areas or targeted to test one particular hypothesis. These studies may be initiated for tumors with a wide variety of etiologic leads that need to be tested, or for tumors for which little is known but which seem right for a "fishing expedition" to generate new etiologic leads.

Several such investigations of breast cancer are in progress. In an analysis of one case-control study, obesity during childhood or adolescence was associated with a reduced risk of both early and late-onset breast cancer. Weight gain in adulthood, however, had a direct relationship to risk of later onset disease, particularly for relatively large, invasive tumors. Analysis of parenchymal patterns on pre-diagnosis mammograms indicated that a simple measurement of the extent of mammographic densities in the breast was a strong and consistent predictor of subsequent breast cancer risks.

In an analysis aimed at uncovering the reasons for the excess of cervical cancer among black women, the risk factors for cervical cancer and the relative risks associated with them were similar for whites and blacks. However, the prevalence of virtually all of these risk factors, except cigarette smoking, was higher in blacks, thus explaining much of the excess risk.

An analysis of the higher rates of bladder cancer among males than females revealed that neither the magnitude of bladder cancer risk factors or their prevalence explained this gender difference. Even in the absence of exposure to cigarettes, occupational hazards or urinary-tract infections, males had a persistent threefold excess risk. Possible explanations for this excess include environmental and dietary exposures not yet identified, and innate sexual characteristics such as anatomic differences, urination habits or hormonal factors.

In a study of penile cancer, the major risk factor identified was a history of phimosis or paraphimosis, particularly when severe enough to require circumcision as a treatment. Other risk factors were consistent with the role of an infectious agent, including a relationship with poor personal hygiene, premarital or extramarital sexual relations, and prior genital diseases (including warts).

Infectious Agents: The discovery of several human retroviruses, notably human T-cell lymphotropic virus type I (HTLV-I) and human immunodeficiency virus (HIV), and rapid strides in the identification of type-specific human papillomaviruses (HPV) in various tumors, have provided impetus to studies of an infectious etiology for some human cancers.

Studies of adult T-cell leukemia/lymphoma (ATL) and HTLV-I in the Caribbean and among Japanese in Hawaii have continued. Infective dermatitis has been identified as an HTLV-I associated syndrome with pre-leukemia potential. Screening of Jamaican blood donors over a one-year period found 2.6% to be HTLV-I positive. A minimum of 45% of recipients of infected blood have seroconverted after a median time of 50 days. Antibody response in seroconversion suggests that core antibody and envelope antibody positivity emerge almost simultaneously. At two years of follow-up, cases of transfusion-associated tropical spastic paraparesis (TSP), various skin abnormalities, and the presence of atypical lymphocytes have been noted among the exposed.

Extensive population surveys and studies of hospitalized patients have raised the suspicion that native American populations may be a reservoir for HTLV-II, but they have not yet found any relationship between infections with this virus and any specific disease.

Studies of HIV infection and AIDS continued to have high program priority. In a study of a registry of HIV seroconverters, homosexual men developed AIDS more rapidly than hemophiliacs, largely because of a high risk of Kaposi's sarcoma among homosexuals compared to hemophiliacs. Older age was associated with a shorter incubation period among hemophiliacs, but not among homosexuals. Among homosexuals the median incubation time from infection to AIDS was nine years.

Among hemophiliacs intermediate markers such as CD4 counts, decline more rapidly in older HIV-infected persons and have a more ominous prognostic significance compared to those in younger persons. Prophylactic therapy of opportunistic infection appears to be postponing clinical AIDS in substantial numbers of severely immunosuppressed individuals, resulting in prolonged survival, and an increasing proportion of HIV-infected persons developing lymphoma as their initial AIDS manifestation. Elevated IgG antibody titers to

Epstein-Barr virus capsid antigen predicted subsequent development of AIDS-associated non-Hodgkin's lymphoma.

A large follow-up study of a Pap smear screening program is providing a variety of results on the relationship of human papillomavirus (HPV) to risk of cervical cancer. In a study of prevalent cases of dysplasia, HPV DNA was detected in 17% of controls, 80% of low-grade dysplasia and 90% of high-grade dysplasia. Detection of HPV 16 or 18 was associated with a 40-fold increase in risk of low-grade dysplasia and over a 100-fold increased risk of high-grade dysplasia. In this same cohort, infection with HPV among women without disease was positively associated with being unmarried, oral contraceptive use, current smoking and nulliparity. Infection was negatively correlated with age, education level, and family income.

In a separate investigation of invasive cervical cancer in four centers in Latin America, there was some evidence of interaction between HPV infection and infection with herpes simplex virus type 2 (HSV-2). Women infected with just HSV-2 were not at increased risk of cervical cancer. However, those co-infected with both viruses had almost twice the risk of those infected only with HPV.

Genetic Susceptibility: The area of host susceptibility to cancer has become one of the most active and exciting in cancer research. Much of the recent enthusiasm has come from remarkable advances in laboratory technology that allow identification of specific genes and their products that might be involved in carcinogenesis. To take advantage of these opportunities, the Branch conducts a broad program of studies focused on a variety of aspects of genetic susceptibility. These include studies of high-risk families to identify mechanisms of carcinogenesis as well as specific genetic events responsible for familial risks. Also, included are a variety of pharmacogenetic studies of differences in metabolism of suspect carcinogens, and investigations of the role of various oncogenes and from a suppressor genes in carcinogenesis outside of the familial context.

In the area of familial cancer, there has continued to be a focus on familial melanoma and the dysplastic nevus syndrome (DNS). In an updated analysis of the original 14 families, the relative risks of subsequent melanoma in those family members with a prior melanoma was 500. The melanoma risks for those members with DNS, but not melanoma, at initial exams was 100-fold higher than the general population risk, and the actuarial estimate of cumulative lifetime risk of melanoma in patients with DNS approached 100%. A case-control study of dysplastic nevi among patients seeing a dermatologist for other reasons indicated that most affected patients also had first degree relatives with dysplastic nevi. Much of the focus in this area has been in verification and further delineation of the gene responsible for the DNS-melanoma syndrome. Our initial localization of this gene to chromosome 1p was the subject of an entire session of this year's Genetic Analysis Workshop. In addition, we are currently studying eight new families to see if we can replicate this observation. Family studies are also continuing on multiple endocrine neoplasia syndrome type I, nevoid basal cell carcinoma syndrome, chronic lymphatic leukemia, and bladder cancer.

Segregation analyses of population-based breast cancer data were performed to clarify inheritance patterns among blacks and by histologic type. Among

blacks, the familial aggregation was consistent with Mendelian recessive transmission of a single major gene. When all races were pooled and analyses conducted by histologic type, ductal carcinoma segregation was consistent with autosomal recessive transmission. In a subanalysis of this group, a recessive gene was sufficient to explain the patterns for postmenopausal cases, while in premenopausal women, transmission was consistent with a dominant major gene.

Metabolic differences, those associated with the P-450 enzyme systems as well as others, as markers of cancer risks are currently under investigation for lung and bladder cancer. The ability to metabolize the drug debrisoquine, a measure of the function of one P-450 enzyme, was related to lung cancer risk in a case-control study. Compared to poor metabolizers, those with an intermediate metabolism had a fourfold excess risk, and those who were extensive metabolizers had a 16-fold excess risk of lung cancer.

Methodologic Studies: Both by design and by the necessities of the types of studies conducted, a variety of methodologic investigations are performed by the Branch. These range from the development and testing of large data collection systems for their applicability to epidemiologic needs, through tests of alternate methods of conducting field investigations, to the adaptation and development of statistical methods for epidemiologic studies.

Data files at the National Center for Health Statistics, Social Security Administration, Health Care Financing Administration, and Veterans Administration have been evaluated and tested for their utility as potential epidemiologic resources.

It is important to note that all components of the Epidemiology and Biostatistics Program contribute to methodologic research, particularly the Biostatistics Branch. In addition, the EEB has embarked on a series of methodologic studies designed to make the rapidly emerging area of biochemical epidemiology, or interdisciplinary studies, more epidemiologically sound. Included in these activities are evaluations of specificity, sensitivity, and predictive value of a variety of newly-emergent laboratory assays. Replicability of these assays, and a determination of the field conditions and storage practices that may influence results, are also receiving attention. Determinants of the values for a variety of these assays are also being investigated in order to identify potential confounding factors, as well as potential sources of bias in their use. While the entire range of activities in biochemical epidemiology is in need of this basic methodologic work, the Branch is currently emphasizing efforts in the areas of genetic markers, biochemical markers of nutritional exposures, laboratory assessments of immune status, markers of exposure to specific chemicals (particularly pesticides), and antibody responses to specific infectious agents.

Most of these methodologic studies are summarized in the sections dealing with the program areas of research. In addition, several studies dealing with the effect of misclassification on estimates of disease exposure for virtually any exposure and disease have been conducted. These investigations have revealed for the first time that under certain conditions random misclassification (misclassification unrelated to disease status), as can typically happen in using surrogate exposure data or blind exposure assessment, can actually lead to spurious risk estimates, as well as obscure risks that are real.

Reviews: A major role of the Branch is to provide comprehensive and critical reviews of etiologic factors in cancer. These reviews take the form of chapters in books, review articles for journals, or, occasionally, reports for various legislative or regulatory bodies. Twenty-eight such reviews have been published in the past year, covering virtually all of the program areas of research covered by the Branch. Reviews of individual cancer sites have included malignant melanoma, nasopharyngeal cancer, multiple myeloma, soft tissue sarcoma, Hodgkin's disease and cervical cancer. Reviews of issues in occupational cancer have included cancer and pesticide exposures in farmers, and herbicide exposures. Reviews of virus-related diseases have included AIDS, ATL, HIV infection, and HTLV-I and -II infections. Specialized topics for review have included the relationship between carotenoids and cancer risks, various aspects of genetics, and treatment-associated second primary cancers. Two overall summaries of cancer epidemiology were also contributed to textbooks.

OTHER ACTIVITIES:

The Branch continued to provide a liaison for epidemiologic research in the National Cancer Program and for environmental cancer studies being conducted in various agencies in the Federal government. A great deal of advice and support was given to clinicians, experimentalists, public health officials, and many other groups. Staff members served on the editorial boards of various journals, and on advisory groups and committees connected with cancer centers, several Federal and State agencies, and other national and international activities. Staff members also helped in preparing reports on chemical carcinogens and other activities coordinated by the International Agency for Research on Cancer and the International Union Against Cancer. Several meetings and projects this year were related to bi-national agreements with the People's Republic of China, Italy, and Japan.

The Branch continued efforts to identify and utilize epidemiologic resources best available at the national level. Initiatives were taken to stimulate and develop cooperative projects with several government agencies possessing routinely collected data resources that can be utilized for epidemiologic studies (e.g., Social Security Administration, Internal Revenue Service, Department of Labor, Bureau of the Census, Veterans Administration and National Center for Health Statistics). Another important activity of the Branch has been the on-the-job training of staff at the postdoctoral level, the supervision of medical students during their elective periods at school, field research opportunities for doctoral candidates at Schools of Public Health, and the assignment of visiting scientists with variable experience in epidemiology.

Although the Branch encourages an atmosphere of academic freedom and the development of new ideas and approaches, innovations undergo critical review and evaluation through several mechanisms. These include frequent section and branch meetings; close contacts with support service and collaborating groups; various formal review mechanisms by internal and external committees; several working groups (e.g., data resources, female tumors, family studies, and drug studies); interagency committees; the Clinical Center Review Committee involving clinical investigations; careful scrutiny of questionnaires and protocols prior to and during clearance through governmental channels; ad hoc external review groups for major studies (e.g., the acrylonitrile and breast

cancer in young women studies); the NIH Coordinating Epidemiology Committee; and a variety of advisory bodies that oversee Institute activities, notably the Division of Cancer Etiology Board of Scientific Counselors.

SUMMARY REPORT

ENVIRONMENTAL STUDIES SECTION

PROGRESS ON RESEARCH CONTRACTS

The studies of the Environmental Studies Section that are supported by the contract mechanism (7 contracts, \$1,881,037) were initiated to clarify the role of various environmental and host determinants in the etiology of malignant neoplasms. Specifically examined are associations of cancer with nutritional factors, drugs, other life-style factors, and prior disease. The areas covered by these contracts included 1) studies examining breast cancer, primarily among younger women, 2) studies on environmental cancer using prepaid health plans, and 3) studies of cancer and drinking water contaminants.

Studies of Breast Cancer, Primarily Among Younger Women (3 contracts):

A population-based case-control studies focused on women under the age of 45 years was initiated in three areas--Atlanta, GA; Trenton, New Jersey; and Seattle, WA. This study was initiated to address effects of three suspect risk factors for the disease, namely oral contraceptive use, alcohol consumption, and dietary patterns, particularly adolescent diet. All incident cases, occurring during the two-year period that began in May of 1990, are being recruited for study. In Atlanta, the age range has been expanded to include women up to the age of 54 years of age. It is estimated that approximately 1,300 cases will be identified as eligible for interview over the study period. For each eligible case, one population control is being chosen through random digit dialing techniques. In Atlanta, an additional control group identified through area control sampling is being included. Both cases and controls are being interviewed in their homes regarding the main hypotheses of interest, as well as regarding a number of other established and suspect risk factors for breast cancer. Following the interview, a variety of anthropometric measurements are being taken. Subjects are also being asked to mail back a self-completed dietary questionnaire, which focuses on usual adult diet. Further, in Seattle, blood specimens are being obtained on a sample of the early stage cases and controls in order to enable a variety of nutrient and hormonal assays.

Studies on Environmental Cancer Using Prepaid Health Plans (3 Contracts):

The main objective of this series of contracts is the establishment of a collaborative research program which provides the E&B Program with resources that can be used to promptly evaluate hypotheses about environmental causes of cancer. This is accomplished by analysis of information in a prepaid health plan utilizing data recorded over many years on large groups of patients having particular cancers or exposures and comparable individuals without the cancer or exposure. Another objective has been to explore the numerous resources for record linkage within these plans in order to exploit unique opportunities for epidemiologic assessment of cancer risks. Because of the nature of prepaid health plan records, the primary hypotheses that can be tested involve those associated with the use of therapeutic drugs, medical conditions, surgical and radiologic procedures, occupations, locations of

residence, and exposures that are highly correlated with any of these variables.

A number of case-control, record abstract studies are currently underway or recently completed. Included is a study of the relationship of specific types of benign breast disease to subsequent breast cancer risk and the role of hormone use in the process, the role of ascertainment bias in an excess of melanoma among workers at the Lawrence Livermore facility, the role of type-specific papillomavirus infection in the progression of cervical dysplasia, and a large study of the relationship between diuretic use and risk of renal cancer. Feasibility efforts are also underway for two cohort investigations, one of the relationship between diet and subsequent cancer risk and the other of the long-term risks and benefits of hormone replacement therapy for the menopause.

Extension of a Case-Control Study of Cancer and Drinking Water Contaminants (1 Contract):

This study was designed to evaluate the cancer risk associated with consumption of drinking water with high levels of contaminants, especially trihalomethanes and other byproducts of water chlorination. Iowa was selected as the study locale. The first part of the study included six anatomic sites of incident cancer: bladder, kidney, colon, rectum, brain, and pancreas. Because of a special interest in bladder cancer, data collection for this cancer site continued for two additional years, to include all bladder cancer cases diagnosed in the period 1988 and 1989 (and frequency-matched controls), as well as cases and controls from the years 1986 and 1987 that were gathered in the first phase of the study.

Data collection is completed, and data reduction, coding, and analysis has started. Modelling of levels of trihalomethanes in Iowa is being used to estimate past exposures of respondents. Included in the study are approximately 4200 cases and 2400 controls. While working on the complex task of developing the drinking water exposure variable, we have evaluated the relationship between bladder cancer in females and reproductive factors, and have noted that ever-parous women are at lower risk than nulliparous women.

ENVIRONMENTAL EPIDEMIOLOGY BRANCH
RESEARCH CONTRACTS ACTIVE DURING FY 91
ENVIRONMENTAL STUDIES SECTION

<u>Institution/Principal Investigator/ Contract Number</u>	<u>Title</u>
Emory University Jonathan Liff N01 CP 95604	Breast Cancer in Women Under the Age of 45 Years
Fred Hutchinson Cancer Research Center Janet Daling N01 CP 95671	Breast Cancer in Women Under the Age of 45 Years
New Jersey State Department of Health Janet Schoenberg N01 CP 95672	Breast Cancer in Women Under the Age of 45 Years
Kaiser Foundation Research Institute Los Angeles, California Harry Ziel N01 CP 11038	Studies on Environmental Cancer Utilizing Prepaid Health Plans
Kaiser Foundation Research Institute Oakland, California Robert Hiatt N01 CP 11037	Studies on Environmental Cancer Utilizing Prepaid Health Plans
Kaiser Foundation Research Institute Portland, Oregon Andrew Glass N01 CP 11009	Studies on Environmental Cancer Utilizing Prepaid Health Plans
University of Iowa Charles Lynch 01 CP 85614	Case-Control Study of Cancer and Drinking Water Contaminants

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04378-16 EEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

U.S. Cancer Mortality Survey and Related Analytic Studies

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: R. N. Hoover Chief EEB NCI

Others: R.T. Falk Health Statistician EEB NCI
J.M. Stump Chief, IRMS BB, DCE NCI

COOPERATING UNITS (if any)

Environmental Protection Agency (Wilson Riggan)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Population Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

0.75

PROFESSIONAL:

0.60

OTHER:

0.15

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

An updated atlas of maps illustrating cancer mortality trends over three decades among nonwhites was published. The rise in rates of oral cavity, laryngeal, esophageal and prostate cancers were 20 to 100 times greater than the corresponding trends among whites. The mortality patterns for most sites showed trends towards increasing geographic uniformity over time. The most notable exceptions to this pattern were the emergence in the 1970s of such rates for prostate cancer among black men in the South Atlantic states, and rising rates for stomach cancer among Native Americans in the Southwest.

In a study of over 2.3 million cancer deaths in counties with fluoridated drinking water supplies, and over 125,000 incident cancer cases in fluoridated counties covered by two population-based cancer registries, we identified no trends in cancer risks that could be attributed to the consumption of fluoridated drinking water.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

R.N. Hoover	Chief	EEB	NCI
R.T. Falk	Health Statistician	EEB	NCI
J.M. Stump	Chief, IRMS	BB	NCI

Objectives:

The overall objective of this project is twofold: 1) through descriptive studies to explore the geographic, racial, ethnic, time-trend and other patterns of cancer mortality in the U.S, and 2) through analytic field investigations in areas of special risk to generate and/or test hypotheses to explain the descriptive variation noted.

Methods Employed:

Methods for the descriptive component of this project involve computer analysis of more than nine million death certificates by site, sex, race, county, and age. the investigation is ongoing, updated each year, and expanding. Data for all causes of death are utilized from 1968. For the analytic phase of this project the usual approach is that of a case-control study of site-specific cancers among residents of the selected geographic areas, utilizing appropriate comparison persons.

Major Findings:

To identify, systematically, the geographic variation and clustering of cancer mortality, the Branch has analyzed U.S. cancer mortality on a county level. In the past, cancer death rates were computed and reported along with maps illustrating the variation. These patterns were also related to demographic and potential exposure information at the county level through correlational or hypothesis-generating studies, thus providing a series of etiologic leads that might explain the variations observed.

In the past year, we have investigated lung cancer incidence patterns from 1969 through 1986 by age, race, sex, and histologic type. The patterns were best described by birth cohort with the rise and fall in squamous cell cancer rates preceding those for small cell and adenocarcinoma by 10 to 20 years within each race-sex group. This histology-specific pattern of rise and fall in rates by birth cohort occurred first for white males followed by black males, followed in turn by white females and then black females. Overall, the rates for squamous cell carcinoma among both sexes and for adenocarcinoma among men were substantially higher for blacks, whereas no racial disparity was seen for small cell carcinomas.

In response to concerns over possible carcinogenicity of fluoride compounds added to drinking water raised by the results of a recent animal experiment, we evaluated 36 years of U.S. cancer mortality and 15 years of cancer incidence data in relation to the fluoridation status of drinking water

supplies for the individual counties under study. Osteosarcomas of the bone were singled out for detailed analysis based on the results of the animal experiment. Among both males and females residing in counties having undergone rapid fluoridation, the relative risks of death from cancers of the bones and joints were the same after 25-30 years of fluoridation as was in the years immediately preceding fluoridation. A similar lack of a relationship to timing of fluoridation was noted for the incidence of bone and joint cancers and osteosarcomas. The mortality and incidence data in this ecologic study allowed an evaluation of the patterns of risks for virtually all forms of cancer in relation to the timing of fluoridation of drinking water supplies. For no type of malignancy was there consistent evidence of a relationship with the patterns of fluoridation. Thus, in a study of over 2.3 million cancer deaths in fluoridated counties across the United States, and over 125,000 incident cancer cases in fluoridated counties covered by two population-based cancer registries, we identified no trends in cancer risks that could be ascribed to the consumption of fluoridated drinking water.

Finally, an atlas of maps illustrating cancer mortality trends over three decades among nonwhites was published. This serves as the comparison volume to a similar atlas illustrating trends in whites. For most cancer sites, trends in U.S. mortality rates for nonwhites resembled those for whites over the 30 years from 1950 to 1980. However, often those that were rising, rose much faster than that seen among whites. For example, the rates of increase among nonwhite males for cancers of the oral cavity, larynx, esophagus and prostate were 20 to 100 times greater than the corresponding trends among white males. Among nonwhite women, breast cancer mortality rates have risen by 1.6% every five years, compared to 0.1% among white women. With respect to geographic variation over time, as noted for whites, the mortality patterns for most sites among nonwhites showed increasing geographic uniformity over time. There were some exceptions to this pattern, the most notable being the emergence in the 1970's of high rates for prostate cancer among black men in the south Atlantic states and rising rates of stomach cancer among native Americans in the southwest.

Publications:

Falk, RT, Pickle, LW, Fonham ET, Correa P, Morse A, Chen V, Fraumeni JF, Jr. Occupation and pancreatic cancer risk in Louisiana. *Am J Ind Med* 1990;18: 565-76.

Hoover RN, DeVesa SS, Cantor KP, Lubin JH, Fraumeni JF, Jr. Fluoridation of drinking water and subsequent cancer incidence and mortality (appendix e). In: Review of fluoride: benefits and risks. Washington, DC: Department of Health and Human Services, Public Health Service, 1991;E2-E51.

Hoover RN, DeVesa SS, Cantor KP, Fraumeni JF, Jr. Time trends for bone and joint cancers and osteosarcomas in the surveillance, epidemiology and end results (SEER) program (appendix f). In: Review of fluoride: benefits and risks. Washington, DC: Department of Health and Human Services, Public Health Service, 1991;F2-F7.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04410-15 EEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Studies of Persons at High Risk of Cancer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	M.A. Tucker	Chief	EEB	NCI
Others:	S.J. Bale	Geneticist	EEB	NCI
	N.E. Caporaso	Biotechnology Fellow	EEB	NCI
	G.L. Shaw	Medical Staff Fellow	EEB	NCI
	A.M. Goldstein	Staff Fellow	EEB	NCI
	C.I. Amos	Staff Fellow	EEB	NCI
	M.C. Fraser	Clinical Nurse Specialist	EEB	NCI
	D.L. Mann	Chief, Immunogenetics Sec.	LVC	NCI

COOPERATING UNITS (if any)

Biological Research Faculty & Facility (T. Williams); Biotech Laboratories (D. Ringer); Westat, Inc. (J. Cahill/J. Rosenthal); IMS (J. Beach); ATCC (R. Hay); Integrated Genetics (K. Klinger)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Family Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

10.7

PROFESSIONAL:

6.2

OTHER:

4.5

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The studies of melanoma-prone families, families with multiple endocrine neoplasia type 1, and nevoid basal cell carcinoma syndrome have continued. Members of the section have contributed data to and participated in the Genetic Analysis Workshop VII. Case-control studies of lung cancer and bladder cancer with biochemical components have continued, and a case-control study of melanoma was initiated and moved into the field. A cohort study of the risk of second cancers after ovarian cancer was continued. Research on mathematical aspects of linkage analysis procedures continued with the development of methods to determine identity-by-descent sharing of genotype in pedigrees and a multivariate linkage procedure.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

M.A. Tucker	Chief, Family Studies Section	EEB	NCI
C.I. Amos	Staff Fellow	EEB	NCI
S.J. Bale	Geneticist	EEB	NCI
N.E. Caporaso	Biotechnology Fellow	EEB	NCI
M.C. Fraser	Nurse Epidemiologist	EEB	NCI
A.M. Goldstein	Staff Fellow	EEB	NCI
G.L. Shaw	Medical Staff Fellow	EEB	NCI
D.L. Mann	Chief, Immunogenetics Section	LVC	NCI
M.T. Landi	Guest Researcher	EEB	NCI

Objectives:

This project endeavors to document the occurrence of cancer in high-risk groups and to study such groups by clinical, epidemiologic and laboratory investigations in an effort to elucidate genetic mechanisms and host-environmental interactions contributing to carcinogenesis; to develop educational materials and provide counseling to study participants; to coordinate the distribution of tissue and blood specimens obtained from high-risk persons to interested investigators for etiologic studies by cytogenetic, immunologic, endocrine, biochemical, tissue culture and other methods; and to apply innovative analytic approaches to these studies, including statistical genetic methods.

Methods Employed:

Protocols for study of high-risk populations are developed, outlining study aims and methods, and are reviewed by the Section's professionals to maximize efficient use of personnel and laboratory resources. Study subjects are interviewed with respect to medical, occupational, and environmental history, as well as familial occurrences of cancer and other disorders, and are examined for clinical features associated with heightened cancer risk. Family medical history is systematically documented utilizing a family medical history questionnaire. Clinical history is documented using vital records and hospital and physician charts, and operative specimens are submitted for review by collaborating pathologists. Data are abstracted, entered, and verified on a computerized record keeping system. Specialized questionnaires are developed for documenting specific etiologic information. Biologic specimens are collected from informative study subjects, stored in biospecimen repositories, and transmitted to collaborating or contract laboratories. For studies of cytotoxic drugs, standard cohort and case-control methods are used.

Major Findings:

PROJECT 1: CLINICAL, BIOLOGICAL AND GENETIC STUDIES OF CANCER-PRONE FAMILIES

Family Studies Resources:

The Family Studies Section shares two contracts with the Viral Epidemiology Section: 1) a biospecimen processing and storage contract for the storage of viable lymphocytes, red blood cells, and serum (Biotech Research Laboratories), and 2) a fibroblast repository for the propagation and storage of fibroblasts (Biological Research Faculty and Facility). The Section also shares three contracts with the Clinical Epidemiology Branch which support genetic linkage studies (American Type Culture Collection, Integrated Genetics, Inc., and University of California at Los Angeles). Cancer Nursing Service continues to provide us with the valuable services of our Epidemiology Research Nurse.

Malignant Melanoma

This project is now in its fifteenth year, employing the interdisciplinary research strategy outlined above. A total of 23 families have now been clinically characterized and specimens collected. We are awaiting the RFLP analysis of eight additional families to try to confirm the location of a melanoma/dysplastic nevus gene at 1p36. The risk of melanoma has been reevaluated in these families with the additional follow up. No melanomas have prospectively occurred in individuals without dysplastic nevi, and there is no significant excess of cancer other than melanoma in these families. An educational pamphlet about sun protection guidelines for children in melanoma-prone families, which was developed by a Cancer Nursing Trainee, is being mailed to study participants.

Bladder Cancer

The younger generation of a previously studied bladder cancer family is now approaching the age at which bladder cancers may be observed. Several members of this family have undergone intravenous pyelography, cystoscopy and metabolic studies to determine which individuals may be at increased risk of developing bladder cancer. A mailing to East Coast urologists was sent, in cooperation with Dr. Marston Linehan of the NCI Surgery Branch, resulting in the ascertainment of one new family, which has also been studied. No new bladder cancers have been identified to date. The data from the metabolic studies are being analyzed.

Hodgkin's Disease and Non-Hodgkin's Lymphoma

Several new families with multiple cases of Hodgkin's disease or non-Hodgkin's lymphoma have been ascertained. Members of these families are being studied using the interdisciplinary research strategy described to attempt to confirm previous suggestions of linkage to the HLA Dr locus.

Nevoid Basal Cell Carcinoma Syndrome:

Studies to find the genomic location of the NBCC gene are ongoing, including linkage studies using DNA markers. In collaboration with the Dermatology Branch, NCI, analysis of the relationship between lifetime sun exposure and development of basal cell carcinomas in affected individuals is underway. A detailed questionnaire has been returned by 70% of 200 family members and sun-exposure information will be analyzed in conjunction with clinical information in the 15 families evaluated thus far.

Multiple Endocrine Neoplasia Type 1 (Wermer's Syndrome):

DNAs have been prepared from individuals in five additional families with MEN1, or variants of the syndrome, and are being tested with several chromosome 11q markers. Linkage analyses are underway.

Ovarian Cancer:

Collaborative efforts were established with groups in Buffalo through Dr. M. Steven Piver at Roswell Park Memorial Institute, and through Dr. Bruce Ponder at the University of Cambridge, England. The purpose of these collaborations is to identify and obtain samples from women in high-risk pedigrees for subsequent genetic linkage studies.

Biochemical Epidemiology of Lung Cancer:

Laboratory studies from the original case-control study of the debrisoquine metabolic phenotype as a risk factor for lung cancer continue. A new assay employing an allele-specific PCR methodology, which recognizes certain mutations in CYP2D6 that were previously misclassified, has been developed. This new assay will be used in the analysis of the stored DNA from cases and controls. Other studies underway include an evaluation of the association between NNK-Lemoglobin adducts and debrisoquine metabolic phenotype.

A large multicenter case-control study of lung cancer and the debrisoquine metabolic phenotype is underway at the NIH Clinical Center; the National Naval Medical Command (NNMC), Bethesda, Maryland; and at the Naval Hospital, Quebec, to confirm the reported association. This study differs from previous studies in that non-diseased control subjects are used. A second goal of the study is to address the effect of surgical resection of the lung tumor on debrisoquine metabolic phenotype. Field work is almost complete.

Biochemical Epidemiology of Bladder Cancer:

Initial results from a collaboration with investigators in Turin, Italy, have been reported. A study of normal individuals was designed to explore a relationship between cigarette smoking (quantity and type of tobacco), 4-aminobiphenyl-hemoglobin adducts, and the acetylation phenotype. In the first report linking carcinogen exposure to both an intermediate marker and a putative genetic susceptibility factor, 4-aminobiphenyl levels were found to be related

to cigarette smoking after adjustment for the acetylation phenotype. In contrast, urinary mutagenicity was associated with the quantity of cigarettes smoked but not with the acetylation phenotypes.

Etiology of Malignant Melanoma:

A multidisciplinary case-control study of the etiology of malignant melanoma has been initiated in Philadelphia and San Francisco. All 1,800 study subjects are undergoing full body skin examinations and interviews. Selected individuals are having nevus biopsies. Melanoma tissue and blood for genetic studies are being obtained on a portion of the melanoma cases. The field work will continue through at least December 1992.

PROJECT 2: THE CARCINOGENICITY OF CYTOTOXIC DRUGS

Employing various strategies, this project is designed in collaboration with the Radiation Epidemiology Branch (REB), NCI, to (1) assess and quantify the cancer risk associated with specific cytotoxic drugs; (2) seek clinically relevant differences in risk among the various agents studied; (3) determine whether cancer risk increases as a function of drug dose; (4) learn whether there is an interaction between cytotoxic drugs and therapeutic radiation in cancer risk; (5) elucidate host characteristics which might permit identifying subgroups of patients which are unusually susceptible to treatment-related cancers; and (6) gain insights into the mechanisms of human carcinogenesis.

Among the strategies employed are: (1) cohort studies of patients with a particular index disease; (2) randomized cohort studies, similar to (1) except that patients are participants in randomized clinical trials; and (3) case-control studies of patients with second cancers.

Ovarian Cancer:

A collaboration with the Gynecologic Oncology Group (GOG) to evaluate the carcinogenicity of cisplatin and doxorubicin as well as to update the previously studied cohorts, is in progress. Abstracting of information from the GOG records progressed slowly under professional service contracts, and an abstractor has been hired under the Westat Support Services Contract to complete the initial abstracting of records of patients developing second cancers or leukemia, and to collect tracking information and initiate tracking of patients without recent follow-up.

Publications:

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CONTRACTS IN SUPPORT OF THIS PROJECT

BIOLOGICAL RESEARCH FACULTY AND FACILITY, INC. (NOI-CP7-1025-00)

Title: Biological Specimen Repository for Patients at High Risk for Cancer

Current Annual Level: \$164,445

Person Years: 2.05

Objectives: To maintain a repository of fibroblasts and tumor cell lines, to grow to bulk culture selected cell lines, and to initiate new cell lines from individuals at increased risk of cancer.

Major Contributions:

The laboratory was sent 62 skin biopsy specimens, four tumor tissues, and one muscle tissue to establish fibroblast and tumor lines. In addition, seven blood samples were sent for EBV transformation of lymphocytes. Of these, cell lines were established on 63 of the 66 solid tissue samples. One did not grow and two were contaminated. Six of the seven blood samples did not yield EBV lines, perhaps because of the poor quality of the blood cells. Fifty-one established cell lines were propagated and refrozen. A total of 231 samples were dispersed to 10 destinations. Thirty-eight cell lines were grown to 1/4 or 1/2 of 1 gm quantities. The cells grown to bulk are used to extract DNA for gene mapping studies.

INTEGRATED GENETICS, INC. (NOI-CP7-1127)

Title: Genetic factors in persons at high risk of cancer (Assay B-DNA Polymorphisms)

Current Annual Level: \$423,879

Person Years: 4.1

Objectives: To provide DNA polymorphism typings on samples submitted for use in genetic linkage studies.

Major Contributions: The lab has thus far performed 1,700 assays on persons with multiple endocrine neoplasia type 1 (MEN1), 737 with basal cell nevus syndrome, 60 with melanoma, and 175 with a variant form of MEN1. The information from this study has contributed to further fine mapping of the gene for MEN1.

REGENTS OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES (N01-CP7-1081)

Title: Genetic Factors in Persons at High Risk of Cancer (Assay A-Protein Polymorphisms)

Current Annual Level: \$52,000

Person Years: .35

Objectives: To provide red blood cell, serum plasma typings for a panel of 30 polymorphic genetic markers for use in genetic linkage studies.

Major Contributions: The laboratory has received samples from 282 individuals in 15 families for analyses of eight hereditary disorders. The results of these studies continue to contribute to further mapping of the genes for multiple endocrine neoplasia type 1, hypertrophic cardiomyopathy and hereditary cutaneous malignant melanoma.

AMERICAN TYPE CULTURE COLLECTION (N01-CP-05684)

Title: Procurement of Transformed Lymphocytes, Lymphoblastoid Lines, and DNA for Genetic Linkage Studies

Current Annual Level: \$320,316

Person Years: 3.8

Objectives: To establish lymphoblastoid lines and to prepare DNA from these lines, fibroblast lines, and tumor tissue for use in genetic linkage and biochemical epidemiologic studies.

Major Contributions: The lab has thus far prepared DNAs from 105 lung cancer cases and controls, 57 persons with hereditary melanoma, and 217 individuals with other genetic disorders.

WESTAT, INC. (N01-CP-05683)

Title: Case-Control Study of Cutaneous Malignant Melanoma Coordinating Center.

Current Annual Level: \$189,727

Person Years: 2.55

Objectives: To develop data collection instruments, train field data collectors, monitor field activities, code and key data for case-control study.

Major Contributions: Westat has prepared a questionnaire, two pathology abstract forms, clinical examination forms, tracking forms, and training materials. They have also developed a laptop computer control selection program, trained field personnel, and monitored field activities. Data coding is just starting.

UNIVERSITY OF PENNSYLVANIA (N01-CP-05682)

Title: Case-Control Study of Cutaneous Malignant Melanoma Field Centers.

Current Annual Level: \$528,440

Person Years: 4.6

Objectives: To identify, interview, and examine cases with cutaneous melanoma and age, sex, race and geography stratified controls. Certain study subjects will undergo phlebotomy, tissue procurement, and/or nevus biopsy.

Major Contributions: Investigators from the field center collaborated on the study design and forms development. Field activities began in January 1991.

NORTHERN CALIFORNIA CANCER CENTER (N01-CP-05681)

Title: Case-Control Study of Cutaneous Malignant Melanoma Field Centers.

Current Annual Level: \$339,191

Person Years: 4.25

Objectives: To identify, interview and examine cases with cutaneous melanoma and age, sex, race, and geography stratified controls. Certain study subjects will have nevus biopsies.

Major Contributions: Investigators from the field center collaborated on the study design and forms development. Field activities began in January 1991.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04411-15 EEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cancer and Related Conditions in Domestic Animals: Epidemiologic Comparisons

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	H.M. Hayes	Veterinary Medical Officer	EEB	NCI
Others:	K.P. Cantor	Epidemiologist	EEB	NCI
	R.N. Hoover	Chief	EEB	NCI
	R.E. Tarone	Statistician	BB, DCE	NCI

COOPERATING UNITS (if any)

Purdue University (R. Richardson), Colorado State University (D. McCurnin), University of Minnesota (C. Jessen), Louisiana State University (H. Casey), U. S. Army (D. Huxsoll)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Environmental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:

1.0

PROFESSIONAL:

1.0

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The veterinary studies area conducts epidemiologic investigations using data compiled by North American veterinary university teaching facilities, the Armed Forces Institute of Pathology, the Department of Defense Military Working Dog Agency, NCI's Registry of Experimental Cancers, and other sources when available. These investigations evaluate the role that environmental factors have in the etiology of cancer in animals, particularly to identify situations where the companion domestic animal may serve as a sentinel for human exposures to environmental carcinogens. Major areas of current interest are the necropsy findings among military working dogs who served in Vietnam, 1968-1973, household and lawn chemical exposures of pet dogs diagnosed with malignant lymphoma, and similar chemical exposures of pet dogs diagnosed with cancer of the lower urinary tract. A case-control study comparing the neoplasm experience at necropsy of 1,200 Vietnam service military working dogs compared with those that served in the U.S. found that Vietnam service dogs had a significant twofold excess of testicular seminoma. Examination of military service records showed an excess risk for seminoma among military working dogs that died in Okinawa as significantly associated with prior service in Vietnam. In an independent investigation, analysis of data from 137 cases of human testicular cancer and 130 controls born prior to 1955 revealed a significant, twofold greater risk of testicular cancer in Vietnam veterans. A case-control study of 491 pet dogs with malignant lymphoma found a significant 1.3-fold association with owner use of phenoxy herbicides and/or employment of commercial lawn care companies. A case-control study of 85 pet dogs with cancer of the lower urinary tract found significant associations with owner use of lawn insecticides and professional lawn care companies, and professional grooming plus exposure to flea and tick dips.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

H.M. Hayes	Veterinary Medical Officer	EEB	NCI
K.P. Cantor	Epidemiologist	EEB	NCI
R.N. Hoover	Chief	EEB	NCI
R.E. Tarone	Statistician	BB, DCE	NCI

Objectives:

To conduct epidemiologic studies to 1) identify situations where companion domestic animals may serve as early predictors of environmental hazards to humans, 2) clarify the role specific home-related factors play in the etiology of cancer, and 3) generate hypotheses for promising areas of research.

Methods Employed:

Analytical studies of animals with suspected environmentally-related cancers are identified from medical record abstracts supplied on contract to the Branch by U.S. and Canadian veterinary university teaching hospitals; selected control animals are selected from the same source. Owner names and addresses are obtained from collaborating institutions and information is sought concerning the home environment, use of yard and garden chemicals, household chemicals, food and drinking water, exposure opportunities, and household history of cancer using a mailed questionnaire. A telephone interview is used in instances of non-response. Descriptive studies utilize veterinary hospital data (2.8 million hospital episodes) to assess risk factors associated with age, breed, sex, neuter status, associated medical conditions, geographic location, and temporal effects.

Necropsy data stored by the Armed Forces Institute of Pathology (AFIP) are analyzed using those military working dogs that served in the U.S. as the referent population. Since all military dogs are necropsied according to a standard protocol, prevalence differences for non-lethal conditions may serve as an estimate of incidence for those who died 1968-1978.

Major Findings:

1. From an analysis of the necropsy findings among 1,200 U.S. military working dogs that served in Vietnam compared with that identified in 800 dogs that served in the U.S., we observed significant elevated risks for testicular seminoma and, independently, testicular dysfunction in Vietnam exposed dogs. An initial unexplained significant excess of seminoma was also observed among military dogs that had died in Okinawa, 1968-1983. Subsequent review of military service records showed this association occurred with prior Vietnam service. Experimental evidence shows testicular dysfunction and impaired spermatogenesis in laboratory animals exposed to certain chemicals used extensively in Vietnam, such as phenoxy herbicides, dioxin (a processing

contaminant of 2,4,5-T herbicide), the herbicide picloram, malathion, and tetracycline, an antibiotic used therapeutically and prophylactically in military working dogs. The testis should be made a priority site in the study of Vietnam experience-related cancers.

2. To test the hypothesis that Vietnam service is a risk factor for testicular cancer in humans, information on military service was evaluated from a case-control study on human testicular cancer. Analysis of data from 137 cases and 130 controls newly diagnosed with cancer, 1976-1981, and referred to one of three Washington, D.C. area hospitals (the Uniformed Services Naval Hospital, the Walter Reed Army Medical Center, the National Institutes of Health Clinical Center) revealed a twofold significant increase of testicular cancer in Vietnam veterans. When analysis was restricted to veterans or was further restricted only to veterans who served during the Vietnam conflict, the association between Vietnam service and testicular cancer risk was slightly stronger, and remained significant. Further studies of testicular cancer should consider service in Vietnam as a potential risk factor.

3. Results of a case-control study (491 cases, 972 controls) of canine malignant lymphoma, a condition considered similar to non-Hodgkin's lymphoma, shows a significant association (OR=1.3) with owner employment of professional lawn care services and/or owner personal application of phenoxy herbicides to lawns accessible to the pet. This association showed a significant positive trend with number of lawn applications per year by the owner. Breeds with a familial predisposition for malignant lymphoma were no more apt to show this association than non-risk breeds. There was no apparent association with exposure to household chemicals, flea and tick dips, sprays, powders, or collars, or being professionally groomed. The present study suggests that human health implications of 2,4-D exposure in the home environment should receive further investigation.

4. Results of a case-control study (85 cases and 972 controls) of lower urinary tract cancer in the pet dog showed a significant 4.9-fold association with owner application of lawn insecticides coupled with the employment of professional lawn care service. Further, a significant twofold association was evident with exposure to professional grooming and flea and tick dips. No apparent association was evident with exposure to phenoxy herbicides, household use of insecticides, or exposure to flea and tick collars, powders, or sprays.

Publications:

Glickman LT, Bergman HL, Buck WB, Cord LC, Fairbrother A, Guarino AM, Hayes HM, Legator MS, McConnell EE, McNelis DN, Temple SA. (Committee on animals as monitors of environmental hazards). Animals as sentinels of environmental hazards. Commission on Life Sciences, National Research Council, National Academy Press, Washington, DC (In Press).

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Hayes HM, Tarone RE, Cantor KP, Jessen CR, McCurnin DM, Richardson RC. A case-control study of canine malignant lymphoma: a positive association with owner use of 2,4-D. JNCI (In Press).

Tarone RE, Hayes HM, Hoover RN, Rosenthal JF, Brown LM, Pottern LM, Javadpour J, O'Connell KJ, Stutzman RE. Service in Vietnam and risk of testicular cancer. JAMA (In Press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04480-15 EEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Studies of Occupational Cancer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	A. E. Blair	Chief, Occupational Studies Section	EEB	NCI
Others:	M. Dosemeci	Visiting Associate	EEB	NCI
	M. R. Gomez	Industrial Hygienist	EEB	NCI
	R. B. Hayes	Epidemiologist	EEB	NCI
	E. F. Heineman	Staff Fellow	EEB	NCI
	L. M. Pottern	Epidemiologist	EEB	NCI
	P. A. Stewart	Industrial Hygienist	EEB	NCI
	S. H. Zahm	Epidemiologist	EEB	NCI

COOPERATING UNITS (if any)

Univ. of NE; Univ. of NC; Univ. of IA; Univ. of MN; Johns Hopkins Univ.; NIOSH; Danish Cancer Registry; Aerobics Institute; NICHD; IARC; Univ. of SC; Univ. of Athens

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Occupational Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

15.6

PROFESSIONAL:

13.1

OTHER:

2.5

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Occupational Studies Section conducts a wide-ranging program of epidemiologic studies to identify the occupational causes of cancer. Currently under investigation include studies of pesticides, benzene, methylene chloride, acrylonitrile, formaldehyde, asbestos, silica, phenol, combustion products, and methodologic investigations to improve exposure assessments. Occupational groups with complex exposures include jewelry manufacturers, laboratory workers, farmers, industrial workers in Turkey, pesticide applicators, embalmers, and workers exposed to benzene, acrylonitrile, and benzidine. Studies of agricultural-related occupations uncovered elevated risks for lymphatic and hematopoietic cancer among farmers. Non-Hodgkin's lymphoma among farmers was strongly associated with use of the herbicide, 2,4-D. Leukemia was associated with several insecticides, particularly if used on animals. Leukemia, non-Hodgkin's lymphoma and nasopharyngeal cancer were elevated among embalmers and funeral directors (among blacks as well as whites) exposed to formaldehyde, while multiple myeloma and non-Hodgkin's lymphoma were associated with solvent exposure among aircraft maintenance workers, particularly among women. An excess of lung cancer among industrial workers exposed to formaldehyde occurred primarily in resin-producing plants and appeared to be due to chemicals other than formaldehyde. Lung cancer was also excessive among silicotics previously employed in the dusty trades in North Carolina. Total mortality, cancer and arteriosclerotic heart disease were greater among workers employed less than one year at the plant than among those employed longer, a phenomenon noted in other studies. This mortality difference appears to be due to lifestyle differences because short-term workers were not assigned to jobs with more intense exposures.

PROJECT DESCRIPTIONNames, Title, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

A. E. Blair	Chief, Occupational Studies Section	EEB	NCI
M. Alavanja	Special Assistant	E&B	NCI
L. Brown	Epidemiologist	BB, DCE	NCI
K. P. Cantor	Epidemiologist	EEB	NCI
M. Dosemeci	Visiting Associate	EEB	NCI
L. W. Figgs	Staff Fellow	EEB	NCI
J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
M. Gomez	Industrial Hygienist	EEB	NCI
R. B. Hayes	Epidemiologist	EEB	NCI
E. Heineman	Staff Fellow	EEB	NCI
R. N. Hoover	Chief	EEB	NCI
Z. Hrubec	Epidemiologist	REB	NCI
J. H. Lubin	Biostatistician	BB, DCE	NCI
L. M. Pottern	Epidemiologist	EEB	NCI
D. A. Riedel	E&B Fellow	EEB	NCI
N. Rothman	Clinical Associate	EEB	NCI
P. A. Stewart	Industrial Hygienist	EEB	NCI
W. Stewart	IPA	EEB	NCI
R. Vetter	EORTC Fellow	EEB	NCI
S. Wacholder	Biostatistician	BB, DCE	NCI
M. H. Ward	E&B Fellow	EEB	NCI
S. H. Zahm	Epidemiologist	EEB	NCI

Objectives: The Occupational Studies Section conducts a comprehensive research program to evaluate the role of workplace exposures in the origin of cancer and to develop methods to improve research in this area. The project seeks to integrate industrial hygiene evaluations and biochemical monitoring into epidemiologic study designs.

Methods Employed: To accomplish program objectives the Section conducts: a) descriptive and hypothesis-generating studies of occupations and industries to identify promising areas of research and to sharpen hypotheses, b) analytic studies with detailed industrial hygiene and biologic monitoring components to evaluate the dose-response relationships, c) industrial hygiene investigations to evaluate workplace exposures and to improve methods of exposure assessment in epidemiologic studies, and d) projects to improve epidemiologic methods and to develop resources for occupational studies.

Major Findings:

Pesticides: Cancer excesses have been noted in occupational groups exposed to pesticides. Despite a lower mortality from heart disease and most cancers than the general population, farmers from developed countries have elevated risks of soft-tissue sarcoma and melanoma of the skin and cancers of the brain, stomach, prostate, lip, and hematopoietic and lymphatic system.

Several of these tumors appear to be increasing in the general population. This suggests that studies of farmers may help identify etiologic factors for these cancers. Many exposures experienced by farmers can also be found in urban environments including pesticides, fuels, engine exhausts, solvents, and dusts. Cancer risks among farmers from pesticide exposures have been evaluated in several midwestern states. In Nebraska, farmers exposed to 2,4-D experienced an elevated risk of non-Hodgkin's lymphoma (NHL) which provided further evidence that this herbicide may be carcinogenic in humans. The risk of NHL rose with the frequency of use of 2,4-D to over threefold among those reporting use for 20 or more days per year. Skin contact is thought to be the major route of exposure for most pesticides and farmers who did not change clothing at the end of the day experienced a greater risk of NHL (odds ratio (OR)=4.7) than those who did (OR=1.1). Farmers who used organophosphate insecticides had approximately a twofold risk of NHL that was independent of the risk from exposure to 2,4-D. Leukemia was slightly elevated among farmers from Iowa and Minnesota (OR=1.2), with the greater risk occurring for chronic lymphocytic leukemia (OR=1.4). Risks of over twofold occurred among farmers exposed to several animal insecticides including carbaryl, coumaphos, dichlorvos, famphur, methoxychlor, nicotine, pyrethrins, and toxaphene. Risks associated with use of insecticides on crops were generally lower, possibly because crop applications occur in less confined spaces resulting in lower exposures.

Formaldehyde: A large proportionate mortality study of embalmers and funeral directors observed a significant excess of lymphatic and hematopoietic cancer among whites (PMR=131), as had been noted by others, and for the first time a similar excess among blacks (PMR=241). Non-significant excesses for nasopharyngeal cancer (PMRs of 189 and 400 for whites and blacks, respectively), which had previously been reported among other occupational groups having contact with formaldehyde, were observed for the first time among embalmers. A nested case-control study of these cancers is underway to evaluate exposure-response relationships and to identify exposures other than formaldehyde that might be involved.

Additional analyses of the data from a large mortality study of industrial workers exposed to formaldehyde indicated that the lung cancer excess was limited to operations involving production of formaldehyde-based resins. Risks of approximately twofold occurred among workers exposed to melamine, phenol, urea and wood dusts and tended to increase with duration of exposure. These and other chemicals used in resin production deserve further evaluation regarding their carcinogenic potential. No excess of any cancer occurred among workers exposed to formaldehyde unless they had exposure to these other chemicals.

A meta-analysis of data from published studies on formaldehyde noted an excess mortality from nasopharyngeal cancer that rose with duration or intensity of exposure. Lung and nasal cancer, two other sites elevated in some studies, did not show an exposure-response pattern.

Other occupational exposures: Lung cancer was elevated among workers in dusty trades from North Carolina with silicosis (SMR=2.6), an excess not diminished

when adjusted for smoking. The risk of lung cancer among silicotics was greater than that among coal miners with pneumoconiosis or among metal miners, suggesting that silica may play an etiologic role.

No significant cancer excesses were observed among a cohort of workers exposed to phenol. Interesting deficits, however, occurred for deaths from arteriosclerotic heart disease, emphysema, and cirrhosis of the liver. The risk of these diseases decreased with increased duration or level of exposure to phenol. Although these may be chance observations, the ability of metabolites of phenol to serve as free radical scavengers suggests a biologic mechanism that might generate such results.

A mortality study of men and women employed at an aircraft maintenance facility noted significant deficits from all cancers combined. Excesses from multiple myeloma and NHL, however, were noted among workers, particularly women, exposed to several organic solvents. The follow-up of the cohort is being extended to further evaluate these findings.

Methodologic investigations: Section investigators devote considerable effort to evaluating and improving industrial hygiene and epidemiologic methods employed in occupational studies. The growing interest in quantitative exposure assessment in occupational investigations was underscored by the attendance at a highly successful International Workshop on Retrospective Exposure Assessment, jointly sponsored by NCI and NIOSH. This conference had nearly 200 participants and the papers presented generated stimulating discussions. Papers from the conference will be published in a special volume of Applied Occupational and Environmental Health. Section industrial hygienists have offered practical considerations on procedures to improve quantitative exposure assessment in retrospective investigations.

Studies of cancer risk from pesticide exposures among farmers rely upon data from interviews. Often it is impossible to interview the case and surrogate respondents are sought. In a comparison of subject and surrogate responses, agreement for use of specific pesticides ranged from 80% to 100% between farmers and their wives. Agreement was lower for frequency of use, but was approximately 60% for most chemicals, indicating that wives can provide useful information on pesticide use by their husbands.

Short-term workers often have higher mortality rates than longer-term workers. Some investigators have suggested this occurs because short-term workers are placed in more highly exposed jobs. Data from a large study of workers exposed to formaldehyde were used to evaluate this issue. Short-term workers experienced greater mortality than long-term workers for all causes of death combined as well as for arteriosclerotic heart disease, cancer, and non-malignant respiratory disease. On the other hand, contrary to a common belief, short-term workers were not assigned to jobs with heavier exposures to formaldehyde than long-term workers.

Other methodologic projects have focused on use of epidemiology in hazard assessment, evaluation of exposure misclassification on risk estimates in hypothetical situations, and effects on relative risks of interview data obtained in case-control studies of cancer and exposure to pesticides.

Other investigations: Analyses of data from a colon cancer screening project revealed an association between smoking and the prevalence of colon polyps. The risk of adenomatous and hyperplastic polyps among smokers were approximately three times that among non-smokers.

A case-control study in Iowa and Minnesota found that risks of leukemia (OR=1.2) and NHL (OR = 1.4) were slightly elevated among persons living within two miles of a factory. The risk of developing leukemia was greater among individuals residing near chemical and petroleum plants, while NHL was associated with stone, clay, or glass factories. Analyses of family history of cancer using data from this study found that having a sibling with hematopoietic or lymphatic cancer increased the risk for leukemia (OR=2.3) and NHL (OR=2.7). Parental history of hematopoietic or lymphatic cancer was not associated with any type of leukemia or NHL.

In a case-control study of testicular cancer, seminomas were associated with employment in professional occupations (OR=2.8), while other germinal cell tumors were linked to production jobs (OR=1.8). Both seminomas and other germinal cell tumors were associated with self-reported exposure to microwaves and other radio waves.

Ongoing investigations: Ongoing investigations are designed to generate new hypotheses, follow-up leads, clarify exposure-response relationships, and improve methods for occupational investigations. A large cohort mortality study in China with a nested case-control component for leukemia capitalizes on the availability of monitoring data to sharpen our understanding of the exposure-response relationship between benzene and this tumor. The cancer risk from acrylonitrile is being evaluated in a study of 25,000 workers in eight plants using or producing this animal carcinogen. A detailed exposure assessment effort will provide quantitative estimates of historical exposures. Cancer mortality from pesticide exposure is being assessed in a study of 45,000 employees of a major lawn care company and a small cohort (3,000 subjects) of herbicide applicators in Kansas. Case-control studies of brain and stomach cancer are being initiated in Nebraska to clarify the excess risk for these tumors in a mortality study of farmers and to identify agricultural factors that might be involved. Potential risks from methylene chloride are being evaluated in case-control studies of cancers of the brain, lung, and pancreas. Data collection has recently been completed for case-control studies of multiple myeloma and brain cancer in Denmark, and multiple myeloma in the United States which include occupational histories to evaluate risk factors in the workplace. The influence of metabolic phenotypes on risk of bladder cancer is being evaluated among workers exposed to benzidine and benzidine-based dyes in the United States. A study in Turkey of a number of cancers offers the opportunity to evaluate risks from occupational exposures in a situation where exposure levels are typically greater than occur in more

developed countries. Methodologic components to develop new approaches and improve exposure assessment techniques for epidemiologic investigations are included in the studies of acrylonitrile, herbicide applicators, and embalmers, and in case-control studies of brain and stomach cancer.

Publications:

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Blair A, Saracci R, Stewart PA, Hayes RB, Shy C. Epidemiologic evidence on the relationships between formaldehyde exposure and cancer. *Scand J Work Environ Health* 1990;16:381-93.

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Heineman EF, Olsen J, Pottern LM, Gomez M, Raffn E, Blair A. In: Potter M, Orams I, eds. *Epidemiology and biology of multiple myeloma: leads for future studies from a case-control study of occupational exposures and multiple myeloma in Denmark*. New York: Springer-Verlag (In Press).

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Kardaun JWPF, Hayes RB, Pottern LM, Brown LM, Hoover RN. Testicular cancer in young men and parental occupation. *Am J Ind Med* (In Press).

Kleinerman R, Littlefield LG, Tarone RE, Sayer AM, Hildreth NG, Pottern LM, Machado SG, Boice JD, Jr. Chromosome aberrations in relation to radiation dose following partial-body exposures in three populations. *Radiat Res* 1990;123:93-101.

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Nee LE, Gomez MR, Dambrosia J, Bale S, Eldridge R, Polinsky RJ. Multiple system atrophy: environmental-occupational risk factors and familial associations. *Clin Autonomic Res* (In Press).

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Riedel DA, Pottern LM, Blattner WA. Epidemiology of multiple myeloma. In: Wiernik PH, Canellos GP, Kyle RA, Schiffer CA, eds. Neoplastic diseases of the blood. 2nd ed. New York: Churchill Livingstone, 1991;5.

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CONTRACTS IN SUPPORT OF THIS PROJECT

WESTAT, INC. (N01-CP9-5618)Title: Support Services for Occupational StudiesCurrent Annual Level: \$1,123,683Person Years: 20

Objectives: To provide data collection and data management services for occupational studies. Activities include abstracting and interviewing, keying, coding, and editing of the data, monitoring and assessing occupational exposures, tracing study subjects, and performing statistical tabulations.

Major Contributions: This contract provides support for many of the occupational investigations conducted by the Section. Studies listed in the publication section receiving support from this contract include the studies of workers in the formaldehyde industries, Nebraska farmers, aircraft maintenance workers, and embalmers. Ongoing studies receiving support include those of lawn care workers, jewelry workers, mortality among U.S. veterans, commercial herbicide applicators, a nested case-control study of cancers of the brain and lymphatic and hematopoietic system among embalmers and funeral directors, workers exposed to acrylonitrile, occupational exposures associated with cancer among Turkish workers, chemists, firefighters, brain and stomach cancer among farmers, and lung cancer among pesticide applicators.

UNIVERSITY OF IOWA (N01-CP-95602)

Title: Development of Exposure Assessment Methods for Studies of Pesticides

Current Annual Level: \$63,302

Person Years: 2

Objectives: To develop procedures which will improve methods to assess pesticide exposures in case-control studies.

Major Contributions: The contract was awarded in April 1989. During the past year a questionnaire has been developed, procedures for monitoring pesticide exposures have been developed, and a pilot study to test all study procedures was completed. Interviewing and monitoring should be completed by the end of the fiscal year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05128-12 EEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Diet and Nutrition in Cancer Etiology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R.G. Ziegler	Epidemiologist	EEB	NCI
Others:	L.A. Brinton	Chief, Environmental Studies	EEB	NCI
	K.P. Cantor	Epidemiologist	EEB	NCI
	G. Gridley	Statistician (Health)	EEB	NCI
	R. Herrero	Visiting Associate	EEB	NCI
	R.N. Hoover	Chief	EEB	NCI
	N.A. Potischman	Staff Fellow	EEB	NCI

COOPERATING UNITS (if any)

Emory Univ (J. Liff), Fred Hutchinson Cancer Res Ctr (J. Daling), NJ State Dept Health (J. Schoenberg), Kaiser Permanente, Los Angeles (W. Finkle), Kaiser Permanente, Portland (A. Glass), NCHS (J. Madans), NIST (N. Craft, S. Margolis)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Environmental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

4.5

PROFESSIONAL:

4.0

OTHER:

0.5

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Recent studies have focused on breast, cervical, and endometrial cancers, utilizing dietary interviews, biochemical methods, and anthropometric measurements to assess exposure. Two case-control studies of breast cancer, one in Asian-Americans and the other in U.S. whites and blacks, are evaluating the role of diet, alcohol, exercise, weight, endogenous hormones, and lifestyle. In the Asian-American study, grandparents' birthplace and subjects' residential history determine a fivefold difference in incidence. Two case-control studies of cervical cancer have been completed. One in the U.S. shows no reduction in risk of invasive or in situ disease with increased intake of carotenoids, vitamin A, vitamin C, or folate. One in Latin America, however, suggests that elevated levels of vitamin C and carotenoids were associated with reduced risk of disease; no effects were detected for vitamin A or folate. A study of vulvar cancer in the U.S. found that intake of alpha-carotene and yellow-orange vegetables might be protective. Since international comparisons demonstrate that endometrial cancer is correlated with fat consumption, a case-control study is investigating etiologic roles of diet and anthropometry. Data from two national surveys have been used to identify nutrients, food groups, and cooking practices associated with a low-fat diet to suggest alternative hypotheses for epidemiologic evaluation. Finally, a liquid chromatography method with high recovery and resolution of individual blood carotenoids has been developed to evaluate further the reduced risk of lung cancer associated with high blood beta-carotene levels in prospective studies.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

R.G. Ziegler	Epidemiologist	EEB	NCI
L.A. Brinton	Chief, Environmental Studies	EEB	NCI
K.E. Brock	IRTA Fellow	EEB	NCI
K.P. Cantor	Epidemiologist	EEB	NCI
G. Gridley	Statistician (Health)	EEB	NCI
R. Herrero	Visiting Associate	EEB	NCI
A. Hildesheim	CEBTP Fellow	EEB	NCI
R.N. Hoover	Chief	EEB	NCI
N.A. Potischman	Staff Fellow	EEB	NCI
C. Schairer	Statistician (Health)	EEB	NCI
M.H. Schiffman	Medical Epidemiologist	EEB	NCI
S.R. Sturgeon	CEBTP Fellow	EEB	NCI

Objectives:

(1) To assess, in human populations, specific hypotheses concerning the relationship of diet, nutrition, and cancer that have been suggested by biochemical, animal, clinical, and epidemiologic studies. (2) To test systematically for associations between diet and nutrition and specific cancers and generate hypotheses about the nature of relationships detected. (3) To develop and validate methods for nutritional epidemiology, including dietary questionnaires, nutrient measures, and analytic approaches. (4) To develop and utilize national nutrition data resources. (5) To elucidate the basic biology of carcinogenesis through studying the influence of diet on cancer in human populations.

Methods Employed:

1. One year of data collection has been completed in a case-control study of breast cancer being conducted in 3 study sites in the United States (see project Z01CP05526-05 EEB). Alcohol intake patterns, physical size and fat distribution patterns, and relative adiposity and physical activity during critical life phases are being assessed through questionnaire and anthropometric measurements. Information is also being obtained about adult and adolescent dietary patterns. Both dietary questionnaires were designed to obtain information about fat, fiber, vitamin C, carotenoid, and methylxanthine intakes. Reports about the subjects' dietary intake are being mailed to participants after receipt of the adult diet questionnaires as a gratuity and an incentive for participation. In an attempt to validate the data on adolescent diet and physical size, information is being obtained from mothers of the subjects. Blood samples are being collected in one study center for micronutrient and hormonal analyses.

2. When Asian women migrate to the U.S., their low rates of breast cancer rise 5-fold toward U.S. Caucasian rates over several generations. Increased dietary fat has been postulated as the cause. To test this hypothesis and

evaluate the role of other characteristics of a Westernized diet, a population-based case-control study was conducted among Asian-American women in Los Angeles, San Francisco, and Oahu. Approximately 600 Chinese, Japanese and Filipino cases diagnosed during 1983-87 and 1,000 controls were interviewed. Subjects were 55 years or younger to facilitate recall of adolescent and childhood diet and lifestyle. No sooner than eight months after diagnosis and treatment, fasting plasma and 12-hour urines were collected for hormone, lipid, and micronutrient determinations; anthropometric measurements were also taken.

3. Data from a case-control study of breast cancer conducted in Buffalo, NY were evaluated for nutrient associations. Dietary data and blood samples were obtained before diagnostic biopsies. Blood samples were analyzed for carotenoids, tocopherols, retinol, cholesterol, triglycerides and selenium. Second blood samples, drawn 3-4 months later, were analyzed for the same nutrients. Information on therapeutic agents was also obtained to assess effects of these agents on nutrients of interest.

4. In the continuation of the follow-up activities within the Breast Cancer Detection Demonstration Project (BCDDP) cohort, a dietary component has been added to the mailed questionnaire. This will enable a number of nutritional hypotheses to be tested. The interview also includes questions on physical activity, alcohol use throughout life, and changes in weight and relative weight.

5. A case-control study of endometrial cancer was completed this year (see Z01CP05526-05 EEB). A food frequency questionnaire administered by interview will be analyzed for dietary intakes of the macronutrients and selected micronutrients, and for dietary patterns. The risk associated with fat distribution patterns and anthropometric indicators of adiposity will be evaluated, together with questionnaire data about weight gain patterns. Arrangements are being made for hormonal and micronutrient analyses of the blood samples collected. Adipose tissue depots from cases and hospital controls from one center are being analyzed for fatty acid composition and compared with fat intake data using plasma and red blood cells as well as dietary data.

6. A dietary component focused on micronutrients postulated to be involved in the etiology of cervical cancer was added to the U.S. case-control study of invasive and in situ cervical cancer, described in project Z01CP05526-05 EEB. Food frequencies and a history of vitamin supplementation were used to estimate the usual adult intake of carotenoids, vitamin A, vitamin C, and folate. To complement this information, blood was collected six months after completion of treatment to measure serum levels of retinol, carotenoids, tocopherols, vitamin C, folate, and selenium, and red blood cell folate.

7. The nutritional component of the Latin American study of invasive cervical cancer, described in project Z01CP05526-05 EEB, is being completed. The sera from early and late stage cases and matched controls have been analyzed for carotenoids, tocopherols, retinol and folate. Cholesterol and triglycerides were assayed in serum samples from two of the four countries involved in the study. Data are being analyzed for the effect of disease

stage on various nutrients measured in the sera. Dietary data have also been analyzed for a variety of micronutrient and food group effects.

8. A case-control study of in situ cervical cancer with matched community controls in Sydney, Australia enabled evaluation of serum selenium levels, adjusted for sexual and reproductive factors.

9. A prospective study is examining the risk of new cervical dysplasia related to human papillomavirus (HPV) infection and other risk factors in a cohort of 18,000 cytologically normal women obtaining Pap smears at Kaiser Permanente, a Portland prepaid health plan. To assess the possibility that low dietary intake of beta-carotene and/or vitamin C may be associated with an increased risk of cervical dysplasia, a self-administered food frequency questionnaire is being distributed to all women with incident cervical dysplasia and their matched controls.

10. The population-based case-control study of vaginal and vulvar cancer, described in project Z01CP05526-05 EEB, collected dietary information and serum samples so that micronutrients hypothesized to be involved in cervical cancer etiology could be evaluated.

11. Data from a multi-center U.S. case-control study of oral and pharyngeal cancer, conducted by the Biostatistics Branch, were used to evaluate vitamin/mineral supplement use and dietary risk factors in blacks.

12. In the case-control study of tumors that occur excessively in blacks (prostate, esophageal, and pancreatic cancer and multiple melanoma), described in project Z01CP05526-05 EEB, macronutrients, micronutrients, food groups, and cooking practices were assessed with a detailed food frequency interview oriented toward both black and white dietary patterns. In addition, selected micronutrients are being measured in sera collected from the controls and the patients with prostate cancer and multiple myeloma.

13. In 1982-84, in cooperation with the National Institute on Aging, other NIH Institutes, and the National Center for Health Statistics (NCHS), the 14,407 adults examined and interviewed 8-14 years earlier in the National Health and Nutrition Examination Survey I (NHANES I) were traced and re-interviewed. The follow-up questionnaire included additional cancer risk factors and a 130-item food frequency interview to complement the single 24-hour dietary recall originally administered. Mortality and incidence follow-up has been completed through 1988 and is now being extended through 1991, which will permit further prospective analyses.

14. Nutrient intake was calculated for a cohort of 17,633 U.S. men (Lutheran Brotherhood Study) who responded to a mailed food frequency questionnaire in 1966. These subjects were then followed until 1986.

15. An analysis of the geographic correlation between selenium in forage crops and cancer mortality in U.S. counties was completed.

16. In collaboration with the National Institute of Standards and Technology (NIST), methodologic studies are being conducted on carotenoids and vitamin C in serum.

Major Findings:

Initial analyses of the Asian-American breast cancer study have focused on the range of breast cancer risk in this heterogeneous population and the relationship of risk to ancestry and migration patterns. The places of birth of the subject and her grandparents, whether East or West, have a major impact on risk, as does the rural or urban nature of the Asian communities where the subject lived prior to migration to the West. Together, these risk factors account for a 5-fold difference in breast cancer incidence, and serve as the focus of the ongoing investigation of correlated lifestyle factors. The 40% reduction in risk observed in women born in the East, compared to those born in the West, is not observed if migration to the West occurred prior to 15 years of age. This finding suggests either that the childhood-adolescence years are critical in determining the risk of breast cancer or that relevant lifestyles, such as diet, are not altered unless migration to the West occurs at an early age. Breast cancer incidence rates in the Asian-American women in this study were intermediate between Asian rates and U.S. Caucasian rates, but higher than anticipated on the basis of historical data.

Analysis of the breast cancer study conducted in Buffalo, NY showed a significant relationship between low plasma beta-carotene and breast cancer risk. Other carotenoids and tocopherols were not associated with risk of disease after adjustment for other factors. Three significant interactions indicated that the combination of low beta-carotene with high retinol, high triglycerides, or high cholesterol resulted in elevated risk of disease. Cholesterol concentrations decreased with advancing stage of disease, suggesting a preclinical effect of disease on blood levels. In the dietary data, vitamin A, fat, and saturated fat were not associated with risk of disease.

In the U.S. case-control study of cervical cancer, women in the highest quartiles of intake of carotenoids, vitamin A, vitamin C and folate had a risk of invasive squamous cell cervical cancer similar to women in the lowest quartiles of intake, although they were consuming 3-4 times as much of the micronutrients. Risk was not reduced by increased consumption of vegetables, dark green vegetables, yellow-orange vegetables, legumes, or fruits, or by high intake of the basic food groups. Recently analysis was extended to the in situ cases since most of the early studies supporting a role for micronutrients in the etiology of cervical neoplasia investigated pre-invasive disease. However, no persuasive associations with the postulated micronutrients were seen. A provocative reduction in risk of in situ and invasive cervical cancer with long-term multivitamin use was noted; however, this finding could reflect associated lifestyles not adequately controlled in the analysis.

Results from the case-control study of invasive cervical cancer in Latin America indicated that risk was associated with low dietary intakes of vitamin

C and beta-carotene. Risk was not related to dietary intake of preformed vitamin A, other carotenoids, or the folate-rich food group. In an analysis of early stage cases, low levels of serum beta-carotene and high levels of gamma-tocopherol were associated with increased risk of disease. Serum samples also indicated no increased risk of disease related to folate concentrations, even among groups with possibly compromised folate status, such as oral contraceptive users and women with multiple pregnancies.

In the Australian study of in situ cervical cancer, serum selenium was not associated with reduced risk, after adjustment for diet, other serum nutrients, smoking, oral contraceptives, and reproductive history. The hypothesized protective effect of selenium is perhaps limited to non-reproductive tumors.

In the vulvar cancer case-control study, micronutrients believed to be involved in the etiology of cervical cancer were not associated with risk, including vitamin A, estimated total carotenoids, beta-carotene, vitamin C, and folate. However, clear increases in risk were observed with decreased intake of dark yellow-orange vegetables and alpha-carotene, with the risks for lowest vs. highest quartiles of intake being 1.6 and 1.7, respectively. This is one of the first analyses to utilize recently available data on the individual carotenoid content of the common vegetables and fruits and suggests that future studies of diet and cancer should evaluate the effect of each of the major carotenoids.

In the oral and pharyngeal cancer study, dietary analyses among blacks found a protective effect (after adjustment for total energy intake) for fruit and vegetable consumption and vitamin C and fiber intake. Patterns of consumption and risk factors were generally similar to those previously reported for whites in the same study. Among whites, cigarette smokers consumed less dietary vitamin C than non-smokers. Vitamin and mineral supplement use was associated with being white, female, living in California, light use of tobacco and alcohol, high education levels, and low body mass. Individual supplemental vitamins, particularly vitamin E, but not multivitamins, were associated with reduced cancer risk. These findings were not modified by dietary intake or age or any of the associated variables. The extent to which these vitamin supplement associations are explained by correlated lifestyle factors remains unclear.

Two nationally representative dietary surveys, the 1987 Health Interview Survey and the 1982-84 Epidemiologic Follow-up Study of NHANES I, were used to examine the nutrient intakes, food groups, and food preparation practices associated with a low-fat diet, and to determine whether patterns differed by age, race, sex, or socioeconomic status. One objective was to identify correlates of a low-fat diet to be evaluated as alternative hypotheses in epidemiologic studies of breast, colon, endometrial, ovarian, and prostate cancer. A second objective was to determine whether public health recommendations to reduce the percent of calories from fat would lead to similar changes in overall diet and nutritional status in all population subgroups. In general, the patterns associated with a low-fat diet were similar across subgroups. While low-fat intake was consistently associated

with high carbohydrate intake, vegetable and fruit consumption was not strongly correlated.

Analyses of the Lutheran Brotherhood Study found no overall association between intake of preformed vitamin A or provitamin A carotenoids and prostate cancer mortality. Total carbohydrate intake was associated with increased risk of stomach cancer mortality.

In an ecologic evaluation using data from U.S. counties, consistent negative associations were found between forage crop selenium levels and cancer mortality for several anatomic sites, specifically lung, rectum, bladder, esophagus, and cervix.

In collaboration with NIST, a liquid chromatographic (LC) technique has been developed to optimize recovery and resolution of the major carotenoids in human serum and plasma. The method is reproducible and relatively rapid, enabling use in epidemiologic investigations with large numbers of samples. None of the LC methods presently in use gives quantitative recovery of the major carotenoids, a situation that can obscure existing associations and produce biased ones. Our method recovers over 95% of the individual carotenoids and can resolve geometric, as well as structural, isomers. The method is now being used to investigate whether the reduced incidence of lung cancer associated with high blood beta-carotene levels in several prospective studies is associated with high levels of many carotenoids. Such a result would suggest that high blood beta-carotene levels are indicators of increased vegetable and fruit consumption and that beta-carotene may not have a unique etiologic role in lung carcinogenesis.

Also in collaboration with NIST, a rapid LC method for accurate and precise measurement of vitamin C (ascorbic and dehydroascorbic acid) in human serum has been developed and characterized. Appropriate conditions for stabilizing and storing vitamin C in serum were documented. Work is continuing to identify blood collection procedures by which physiologic levels of dehydroascorbic acid can be maintained in order to investigate whether this compound acid exists in meaningful levels in human serum or is primarily an artifact of blood collection procedures.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05400-08 EEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Epidemiology of Human Lymphotropic Viruses: ATL, AIDS and Cancer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

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COOPERATING UNITS (if any) U.W. Indies, Kingston (B. Hanchard); Caribbean Epidemiology Centre (C. Bartholomew); Research Triangle Institute (B. Harris, M. Barnett, A. Levin); Program Resources, Inc. (D. Waters, J. Drummond); U. of Alabama (G. Shaw);

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Environmental Epidemiology Branch

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Viral Epidemiology Section

INSTITUTE AND LOCATION

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TOTAL MAN-YEARS:

12

PROFESSIONAL:

10

OTHER:

2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

Retroviruses are important agents in the etiology of cancers and other human diseases. Human T-lymphotrophic virus type I (HTLV-I) causes adult T-cell leukemia as shown by epidemiologic and experimental data. Based on ATL incidence data from a population registry, early life exposure is critical for subsequent disease occurrence. Infective dermatitis was recognized as an HTLV-I associated syndrome with pre-leukemic potential. Spontaneous lymphocyte proliferation of peripheral blood cells from HTLV positive individuals may provide new insights into the process of leukemogenesis. American Indian populations in Northern, Central and South America may be the natural reservoir for HTLV-II infection, a virus previously associated with parenteral drug abuse. No specific disease association with HTLV-II, has been identified. Studies of HIV transmission have provided new insights of relevance to vaccine development by the finding that maternal-to-child transmission is prevented by high affinity antibodies to HIV in the mother's serum. The major cofactor associated with more rapid progression to clinical AIDS is older age, while there are no major differences by risk group and calendar time of infection. Intermediate markers such as CD4 count decline more rapidly in older HIV-infected persons and have a more ominous prognostic significance compared to those in younger persons. Prophylactic therapy appears to be postponing clinical AIDS in significant numbers of severely immunosuppressed individuals. With prolonged survival, an increasing proportion of HIV coinfecting persons will develop lymphoma as their initial manifestation. DNA tumor viruses are possible cofactors in HIV-1 related malignancy, and the newly discovered human herpesvirus 6 may have oncogenic potential.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliation of Professional Personnel Engaged on this Project:

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M. Madeleine	Research Assistant	EEB	NCI
A. Saracco	Guest Researcher	EEB	NCI
L. Diamondstone	Epidemiology Training Program	EEB	NCI
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I. Magrath	Research Investigator	PB	NCI
E. Jaffe	Chief	LP	NCI
D. Ablashi	Microbiologist	LCMB	NCI

Objective:

The objective of the Viral Epidemiology Section is to generate and test hypotheses concerning the role of pathogenic human viruses in the etiology of cancer and to expand our knowledge of the AIDS epidemic, with a particular focus on cancer.

Methods Employed:

Studies undertaken by the Viral Epidemiology Section involve a series of research approaches. Cross-sectional surveys and descriptive case series are employed to provide initial information on the distribution of virus exposure and the nature of related diseases. A major tool for analysis is the prospective cohort study which provides information on the natural history of infection, the frequency of disease occurrence resulting from exposure, and the cofactors which modify risk. To analyze specific risk factors for infection or outcome, case-control studies are employed. A variety of biochemical markers are utilized to define intermediate outcomes or markers of high risk.

Major Findings:

PROJECT 1: Human T-cell Lymphotropic Viruses (HTLV-I and HTLV-II)

To support studies of HTLV-I and -II, a series of research contracts have been established with the University of West Indies at Kingston, Jamaica; the Caribbean Epidemiology Research Center, Port-of-Spain, Trinidad; and Gorgas Memorial Institute, Panama City, Panama.

Adult T-cell Leukemia

A registry of adult T-cell leukemia (ATL) was established in Kingston, Jamaica in January 1984 and in Port-of-Spain, Trinidad in February 1985, with over 180 cases of non-Hodgkin's lymphoma enrolled to date. In Jamaica, classification of NHL cases has revealed that two-thirds are T-cell, of which over 50% are HTLV-I positive, indicating a 10- to 20-fold increase in risk for ATL among persons seropositive for HTLV-I. Epidemiologic risk factors are being evaluated, and preliminary analysis suggests early life exposure is key to subsequent leukemia risk. Laboratory studies have identified evidence that HTLV-I regulatory gene message expression is detectable in ATL tissues. Expression of messenger RNA for various lymphokines has also been evaluated and a unique ATL-specific profile has been detected, suggesting that overexpression of tumor growth factor beta may correlate with ATL occurrence. Since this material is immunosuppressive, this finding supports the concept that immunosuppression may play a role in ATL pathogenesis.

In the United States, an ATL registry continues to enroll new cases referred to the NCI for evaluation and to record features of cases reported in the literature. Thus far, 168 cases have been recorded by the Registry and 83 of these have been confirmed using an algorithm recently developed by the EEB. An international workshop involving investigators from geographic locales endemic and non-endemic for ATL has initiated an effort to unify diagnosis and classification of the disease based on the algorithm developed by the American ATL registry. Laboratory techniques able to identify HTLV-I in paraffin blocks of ATL tumors have been successfully applied, improving the documentation of cases.

Tropical Spastic Paraparesis

HTLV-I is linked to a demyelinating neurologic condition, tropical spastic paraparesis (TSP). In Panama, a registry of neurologic conditions documented the frequent occurrence of TSP and its association with HTLV-I. Noteworthy is the contrast between the frequent occurrence of TSP and the infrequent occurrence of ATL, which raises the possibility that there are virus strain differences or host response differences in disease occurrence. In conjunction with collaborators from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), Jamaica and Trinidad, we are conducting an analytic case-control study of TSP utilizing a questionnaire patterned after our questionnaire utilized to study ATL. This parallel study seeks to define similarities and differences between TSP and ATL which may provide clues to latency and risk factors for these HTLV-I-related diseases. Laboratory studies show that lymphocytes of TSP cases and HTLV-I-positive normal subjects undergo spontaneous lymphocyte proliferation. An array of

lymphokines, including TNF-B are overexpressed in TSP in a pattern distinctive from that of ATL. These abnormalities may play a role in disease pathogenesis.

Infective Dermatitis

A significant new finding is the identification of a new HTLV-I associated condition called infective dermatitis (ID). This condition has many features of an immunodeficiency disease, and the occurrence of ATL in some patients with this syndrome raises the possibility that ID is a preleukemic syndrome. Further study is underway to characterize the underlying role of HTLV-I in this syndrome and its relationship to ATL.

Foodhandler Study

In Jamaica, 13,500 food service employees (foodhandlers) have been tested for HTLV-I and a subset is targeted for follow-up. The major findings from the cross-sectional survey include: a) a marked female excess in prevalence for all adult age groups; b) generally uniform geographical distribution of HTLV-I prevalence across the island of Jamaica, except for lower rates linked to residence at higher elevation for both males and females; and c) an association between markers of lower socioeconomic status and higher HTLV-I prevalence. It is possible that the geographic and socioeconomic correlates might be linked to ecologic factors which activate the immune system and increase the likelihood that an exposed person will become infected.

Phase 2 of the foodhandler survey is a nested case-control study of risk factors for seropositivity. Two hundred fifty healthy seropositives were frequency-matched by age, sex, and locale of current residence and were followed up 2 years after the initial survey. Of interest is the fact that among the first 150 seropositives to be screened, five had neurologic symptoms or signs, and one of these has been confirmed as a case of TSP. Lymphocyte samples from these patients have also been tested for spontaneous lymphocyte proliferation (SLP) and elevated SLP was seen in seropositives. Seronegatives had SLP rates significantly higher than U.S. controls but less than those observed in the seropositives. This elevation in background SLP might be associated with heightened susceptibility to HTLV-I if an activated T-cell marker is involved in virus attachment to target cells.

Hepatitis Cohort

In Trinidad and Tobago, an occupationally-based cohort of 1,729 persons had been assembled for a study of hepatitis prevalence in 1982. Seroprevalence was higher on the small island of Tobago (17/149=11.4%) than on the larger island of Trinidad (33/1,025=3.2%). The use of an outdoor water supply and an outdoor toilet were both correlated with HTLV-I seropositivity on Tobago, suggesting that lower socioeconomic status may be linked to the higher rates on the small island. HTLV-I seropositivity was correlated with the presence of antibodies to hepatitis B, which appeared to be a surrogate for male-to-female sexual transmission.

Japan-Hawaii Cancer Study Cohort

Serologic analysis of a cohort of Hawaiian men from the Japan-Hawaii Cancer Study showed high rates of seropositivity among Japanese American residents with links to the viral-endemic areas of Japan and Okinawa. Data from a follow-back to this cohort suggests that rates of infection may be declining in the next U.S.-born generation. Household transmission appears to be linked to male-to-female, presumably sexual, transmission and higher virus antibody titer in husbands is associated with higher rates of infection in female spouses. A variety of health effects, including mild anemia and lymphocytosis as well as a decline in study participation in older persons with elevated HTLV-I antibody titers, suggests that yet-to-be-defined morbidity is associated with HTLV-I. Genetics may play a role in ATL causation. The two cases of ATL in the cohort are brothers, who developed the disease seven years apart.

Maternal to Child Transmission

Over 9,000 Jamaican women were screened in a survey of maternal-child HTLV-I transmission, and 336 are enrolled in the prospective follow-up phase. Fifteen children of HTLV-I positive women have already seroconverted. A syndrome of persistent lymphadenopathy has been documented in children of seropositive mothers, and this syndrome may be an early sign of HTLV-I infection. Maternal and child biologic specimens are being analyzed by different laboratory methods to identify factors that enhance transmission and to measure possible immunodeficiency in seropositive children.

Transfusion Transmission of HTLV-I

Screening of Jamaican blood donors over a one-year period found 2.6% to be positive. A minimum of 45% of recipients of HTLV-I positive blood units have seroconverted after a median time of 50 days. No recipients of negative blood units have seroconverted. Whole blood and cell components of blood, but not cell-free materials, are linked to seroconversion. Longer shelf life is associated with decreased seroconversion. Antibody response in seroconversion suggests that while patterns vary from case-to-case, core antibody and envelope antibody positivity emerge almost simultaneously. At 2-year follow-up, cases of transfusion-associated TSP, various skin abnormalities, and the presence of atypical lymphocytes have been noted. Continued follow-up is planned.

HTLV-I and HTLV-II in Drug Abusers

Sera collected from a cohort of parenteral drug users in New Orleans with a high rate of HTLV-II infection were used by several laboratories to develop serologic assays to distinguish HTLV-I from HTLV-II infection. This cohort was followed-up to describe the natural history of HTLV-II infection. As this infection has not been linked with any disease, a hospital survey was undertaken in Charity Hospital in New Orleans. Over 3,000 sera were tested and the HTLV-I/II prevalence was 3%. No single disease was associated with seropositivity. This finding has an important public health impact, as half of HTLV-I/II seropositive blood donors in the United States are infected with HTLV-II. Cells from these HTLV-II positive drug abusers

exhibit spontaneous lymphocyte proliferation but at a lower level than that seen for HTLV-I. SLP was independently associated with frequent numbers of needle exchange episodes, suggesting that antigenic stimulation might be a factor in the activated lymphocyte profile of these individuals.

We also examined sera collected from drug abusers in 6 cities between 1972 and 1976 to determine if retroviruses were present in this period. While none of these drug abusers had antibodies to HIV, a high prevalence of antibodies to HTLV (mainly type II) was found. Using records of these subjects in the Veterans Administration and Social Security systems, we were unable to document any adverse effect of being infected. HTLV-I/II was surveyed in multiple sites in the mid-Atlantic and Central region of the United States and highest rates were found in the mid-Atlantic region. In another study being conducted with the National Institute on Drug Abuse involving serial cross-sectional surveys, seroprevalance was higher in drug users than in the general population (11.5 % versus < 1%). Coinfection by HIV-1 and HTLV-I/II did not occur more frequently than expected by chance. Another cross-sectional survey of drug abusers in New Jersey noted significant racial, geographic, drug abuse, and sexual cofactors associated with HTLV-II seropositivity.

HTLV-II in Native Americans

A major discovery is the recognition that native American populations are an endemic reservoir of HTLV-II infection. This finding was first noted in Panama where, for a number of years, aberrant serology suggested that an HTLV-related virus might be present. The recognition that Guyami Indians in Northwest Panama had a high prevalence of HTLV prompted collaboration with colleagues from the Centers for Disease Control. Based on virus culture and polymerase chain reaction (PCR) analysis, the only virus type identified was HTLV-II. Currently, further follow-up is underway to evaluate the epidemiology of the virus in this population. Seminole Indians of South Florida and several Indian tribes in central Brazil also appear to harbor the virus. In this population, seropositivity rates increase with age and female rates are higher than those in males. Additional native American populations are being tested for HTLV-II utilizing available collections of serum from various established serum banks.

PROJECT 2: HIV AND AIDS

Mathematical Modeling

We continued our close collaboration with the Epidemiologic Methods Section, reporting backcalculation estimates of the prevalence rates of HIV infection for various groups in the United States. We estimated that there were 411,000 to 756,000 infected persons in 1985, including 266,000 to 492,000 homosexual men, 69,000 to 136,000 intravenous drug abusers, and 11,000 to 26,000 persons infected through heterosexual contact. The estimated 1985 prevalence rates among persons aged 15 to 55 years were 0.31% in whites, 0.78% in Hispanics, and 0.81% in blacks. An estimated 32,000 to 66,000 women were likely infected, with prevalence rates 5-fold higher in Hispanic women and 10-fold higher in black women compared to white women. We estimated that 992,000 persons were infected by July 1987, although the plausible range was 700,000 to 1.4 million. We also reported detailed analyses of AIDS incidence trends and zidovudine use in demographic and HIV-transmission

categories. Zidovudine use and favorable AIDS incidence trends correlated directly, with the most extensive use and most favorable trends in white homosexual men in New York City, San Francisco and Los Angeles. By the middle of 1988, little or no zidovudine was used by intravenous drug abusers and other largely black and Hispanic groups, and AIDS incidence in these groups continued unabated through 1989. The findings suggested that broader application of therapy might further retard the incidence of AIDS, especially in intravenous drug abusers, persons infected through heterosexual contact, minorities, women, and persons infected outside major metropolitan areas.

Hemophiliacs and Their Female Sexual Partners

The hemophilia cohort, first evaluated in 1982, was expanded to nearly 2000 subjects by adding four centers in Europe (Munich, Geneva, Vienna, and Athens) and the recruitment of all subjects potentially exposed to HIV at the University of North Carolina. Analyses have focused on four areas. Seven of 237 steady female sexual partners were found to be infected with hepatitis C virus (HCV), four of whom were co-infected with HIV. This co-infection rate is sixfold higher than expected, suggesting that HIV and HCV appear to be co-transmitted, perhaps due to reactivation of HCV in the setting of immune deficiency. Laboratory markers, clinical conditions, and age were found to independently predict AIDS, although the specific associations and patterns differed for children and adults, suggesting potentially important clinical and biological differences by age. The impact of AZT and other therapies on national AIDS incidence rates is described in more detail elsewhere in this section, as are the incidence rates of cancers (especially non-Hodgkin's lymphoma) in the hemophilia cohort.

Homosexual men

The International Registry of Seroconverters provided data for a report summarizing AIDS incubation in nearly 1200 subjects from 30 different cohorts. This report examined incubation by risk group, age, place and time of seroconversion. Within the largest group, homosexual men, incubation appeared to be similar in different places and among persons who seroconverted at different times. Homosexual men developed AIDS more quickly than hemophilic persons, largely because of a high risk of Kaposi's sarcoma, an AIDS-defining illness with a much lower incidence in hemophilic persons. Older age shortened the incubation period among hemophilic persons but among homosexual men the differences by age were not extreme. The approach to analysis was conservative, resulting in valid comparative data but also possible shortening of the apparent incubation period. However, comparison of the incubation period within this study (by far the largest) with results published from other groups suggests that the incubation period may be slightly shorter than reported elsewhere, with the median among homosexual men being about nine years. Throughout the year, we have updated the data set in preparation for a new analysis of the incubation period and now have more than 2400 subjects.

The recognition that antiviral therapy can delay the development of AIDS has promoted interest in staging systems to determine who will benefit most from

therapy. We have shown that biochemical markers of immune activation (beta-2-microglobulin and neopterin) add additional predictive value to the CD4 cell counts and ratios. In addition, the levels of CD4 counts and T-cell ratios soon after infection can predict who is likely to develop AIDS within the first few years.

Mothers and Infants

In collaboration with the National Institute of Child Health and Human Development, we have continued to enroll and follow HIV-positive and -negative pregnant women and their offspring. We are continuing to pursue our original observation that serologic response of the mother to the HIV viral envelope influences the likelihood of transmission by comparing serologic reactivity with peptides specific to various epitopes of the virus. Recent data analyses have shown that HIV infection is not associated with frank complications of labor or delivery, nor with any apparent complications in the neonates. However, the infants born to HIV-infected women do not grow or gain weight at the same rate as those born to HIV-uninfected women, with the differences appearing to be limited to the 29% of exposed infants actually infected.

We also initiated The International Registry of HIV-Exposed Twins to gather and analyze data from all available sources around the world. During the last three months of 1990, 35 contributors in seven countries provided data on 83 infant sets (1 triplet). Of 50 sets with complete data, perinatal transmission of HIV was strongly associated with being born first, irrespective of route of delivery or zygosity. This finding suggests that proximity to the cervix increases the risk of becoming infected, probably during labor or parturition. Additional sets of twins and follow-up data have been received and will be analyzed.

Kaposi's Sarcoma

Kaposi's sarcoma continues to be a major problem in homosexual men despite its decline relative to the incidence of AIDS-associated opportunistic infections. We have described a falling relative incidence in all parts of Europe. Further analysis did not suggest any regional environmental factors influencing the rate of Kaposi's in different populations of Europe. In a second project, we have described in detail the histology of Kaposi's sarcoma in HIV-negative (endemic) cases from Greece. To our surprise, we noted retrovirus-like particles in several Kaposi's sarcoma tumors on electron microscopy. Efforts to further characterize this agent and determine its relationship to Kaposi's sarcoma are underway.

Lymphoma and Other Cancers

We have noted that lymphoma is an increasing problem among AIDS cases and promises to be an increasing contributor in years to come since the incidence of opportunistic infections is declining with better prophylaxis. We estimate that in 1994 over 4,000 excess cases of lymphomas (over expected from the pre-AIDS era) will occur, constituting approximately 10 percent of all non-Hodgkin's lymphomas. Already, lymphomas are as frequent as Kaposi's sarcoma, even in homosexual men. There is no evidence of other cancers occurring in excess. However, we note that immunosuppressed homosexual men have a high frequency of human papillomavirus production as detected (by hybridization) in anal areas compared to immune competent

men. Since papillomaviruses are thought to increase the risk of malignancy, we are concerned that this increase in detection could manifest as an increase of anal cancer at a later date.

We found that elevated IgG antibody titers to Epstein-Barr virus capsid antigen predicted subsequent development of AIDS-associated non-Hodgkin's lymphoma (NHL). Preliminary studies in NHL cases associated with allograft transplantation had similar findings. We have evaluated the incidence and characteristics of NHL and other cancers occurring in our homosexual and hemophilia cohorts. Both groups evidence increased risk of NHL which markedly accelerates 8 years after seroconversion. Apart from Kaposi's sarcoma, other tumors are not apparently increased. These studies will be expanded with a new cohort study which will seek to enroll the majority of HIV-infected hemophilia patients in the United States as well as from selected international sites, including Canada and some European areas. Follow-up for malignancy outcomes will provide a quantitative mechanism to define not only the spectrum of HIV-associated malignancies and their subtypes (e.g., lymphomas), but also provide a means to quantify the risk for cancers not yet linked to HIV infection.

Human papillomavirus (HPV) is a sexually transmitted virus. We examined transmission to the anal canal in homosexual men in both the United States and Denmark. Detection by standard hybridization techniques was markedly higher in men with HIV-induced immunosuppression than those who were normal and correlated with level of immune dysfunction. However, by the much more sensitive technique of PCR, detection was about equal, suggesting that immunosuppression is associated with active replication of HPV. Anal infection with human papillomaviruses of several genotypes was more frequent in homosexual men who were co-infected with HIV, especially those with lower levels of immunity as measured by CD4-lymphocyte counts. It was also noted that abnormalities on anal Papanicolaou smears were strongly related to active HPV infection.

Behavioral Studies

The risk of retrovirus transmission depends in large part on sexual behavior. We have undertaken a survey to understand who responds to sexual behavior and whether the approach biases responses obtained. The results suggest that although biases occur, they probably do not greatly influence the overall outcome of surveys, perhaps because persons of both conservative and non-conservative behaviors exclude themselves at a similar rate. Overall, 16 percent of subjects engaged in potentially risky behavior, such as sexual contact with prostitutes and other groups at high risk of HIV infection, reported unprotected sexual encounters. In a survey of behavior that might spread infection in Africa, we found a high frequency of potentially risky practices, many of which are rooted in the poorer socioeconomic development of these societies.

AIDS is increasingly diagnosed among heterosexuals. We therefore undertook studies of heterosexual behavior among American women, showing that women from more recent birth cohorts had significantly more sexual partners than women in older birth cohorts and numbers were also higher as a function of age. At least through 1984, the trend towards having more sexual partners was increasing despite AIDS education campaigns. We have recently surveyed a sample of the entire Danish population in order to establish a behavioral profile there to learn if the methodology of recruiting participants in these surveys will impact on who responds and what they will say.

Molecular Epidemiology

An HTLV-IIIB infected laboratory worker has continued to be followed on a regular basis and serial virus isolations obtained. Sequence analysis of the isolates documents that a portion of the genome coded for the viral envelope changes about 1% per year and these changes correlate with changes in immune response to the virus. Virus isolates from individuals followed over extended periods of time have been obtained, including the original HIV virus isolate from "Bru" in Paris which was shown to be distinctive from HTLV-IIIB and whose serial sequences over time diverge from IIIB. Other virus isolates from different parts of Africa are being made and sequenced to evaluate the variation in viruses from this region compared to isolates from the United States. Type-specific serologic evaluation is being conducted to look at isolate-specific neutralization and cross-neutralization. These molecular epidemiologic efforts are essential for future efforts to develop an effective HIV vaccine.

International Studies

A number of studies are underway to monitor seroprevalence of HIV-1 and -2 and related retroviruses and to evaluate trends in seroincidence where possible. In Tanzania, a survey of a rural area adjacent to a small town demonstrated that seroprevalence is higher in the urban area but that rates have dramatically increased in the last several years. In Nigeria, an extensive survey of female prostitutes documented significantly elevated rates, which are highest in lower class prostitutes and tenfold higher than in prior surveys, again supporting the concept of rapidly increasing spread of the virus. In Ghana, both HIV-1 and variant forms of HIV-2 have emerged in recent time periods. In Jamaica, rates of HIV-1 in sexually transmitted disease clinics have escalated eightfold over the last 3 to 4 years. These prospectively followed populations may provide a critical window to the future course of the epidemic and create opportunities to identify populations where intervention and vaccine trials might be considered.

PROJECT 3: Lymphotropic Herpesviruses and Cancers

Characterization of Burkitt's lymphoma (BL) into "classical" (also called "endemic") and "non-classical" BL was achieved by molecular studies which demonstrated that the classical form had a consistent chromosome translocation, activation of the *myc*-oncogene and an immunoglobulin rearrangement that were consistent and different from the more heterogenous "non-classic" (sporadic) form of Burkitt's lymphoma. A potential relationship between human herpesvirus-6 (HHV-6) and lymphoma was

initially suggested by serologic studies which showed elevated antibody titers in several human malignancies, including Hodgkin's disease (HD) and acute lymphocytic leukemia (ALL), and by the detection of viral genome in three human B-cell lymphomas. In the past year we showed that the earlier reported associations were artifacts of treatment (for HD) and age (for ALL). HHV-6 serology may be used prognostically in HD patients, however, since antibody titers rise with progressive disease. Other serologic studies show that HHV-6 titers vary geographically, with Asians having significantly lower antibody levels (and perhaps prevalence) than U.S. Caucasians or Ghanaians. A newly described HHV-6 antibody to an early protein was first evaluated on a series of serum samples from the Tumor Virus Epidemiology Repository (TVER) and showed a strong association with BL and HD. Potential applications of this discovery are being investigated.

We are also using reagent sera from the TVER (that have been well characterized for herpesvirus antibodies) to evaluate the patterns of antibody to another T-lymphotropic herpesvirus (HHV-7) recently isolated from the lymphocytes of a patient with chronic fatigue syndrome. The pattern of antibody is markedly different from that of EBV or HHV-6, thus far showing depressed levels in sera from lymphoma patients in comparison to normal controls.

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CONTRACTS IN SUPPORT OF THIS PROJECT

RESEARCH TRIANGLE INSTITUTE (N01-CP8-5603-00)

Title: Epidemiology Surveys for Human Retroviruses

Current Annual Level: \$503,667

Person Years: 3

Objectives: Undertake epidemiologic surveys and studies of human retroviruses and retroviral diseases in various geographic locale of the world.

Major Contributions: In Africa cross-sectional surveys have documented rates of HIV-I infection that are higher than previously reported in the same populations. In South and Central America studies have identified focuses of HTLV-I/II infection. In the South Pacific studies are focusing on lymphoma in relationship to a variant form of HTLV-I viruses.

CARIBBEAN EPIDEMIOLOGY CENTER (N01-CP6-1022-00)

Title: Epidemiology of Human T-cell Leukemia/Lymphoma Virus in Trinidad and the Caribbean Region.

Current Annual Level: \$207,129

Person Years: 4

Objectives: To support studies in the Caribbean region on the relationship between HIV and HTLV-I.

Major Contributions: HTLV-I-associated leukemia/lymphoma and neurologic disease are being studied in incidence based case-control studies. Surveys of opulations document a rising incidence of HIV-I infection and high rates of HTLV-I in selected populations.

RESEARCH TRIANGLE INSTITUTE (N01-CP9-5612-00; formerly N01-CP6-1013-00)

Title: Support Services for Studies of HIV and Related Viruses.

Current Annual Level: \$1,211,670

Person Years: 17

Objectives: To support HIV and HTLV studies with research support personnel and computer facilities.

Major Contributions: The personnel of the contract have provided excellent support in all field projects and in computer analysis.

UNIVERSITY OF GHANA (N01-CP8-5612-00)

Title: Studies on the Epidemiology of Potentially Oncogenic and Immunosuppressive Viruses in West Africa.

Current Annual Level: \$45,000

Person Years: 4

Objectives: To monitor HIV and the prevalence of other human retroviruses and to determine their relationship to human disease.

Major Contributions: HIV has increased over the years of the contract through prostitutes returning home from neighboring countries. Cancers associated with HTLV are not increased.

BIOTECH RESEARCH LABORATORIES, INC. (N01-CP9-5663-00; formerly N01-CP2-1121-00)

Title: Laboratory Support for Specimen Processing and Storage of Biological Specimens from Persons at High Risk of Cancer.

Current Annual Level: \$511,995

Person Years: 6

Objectives: To organize, aliquote, store and ship specimens obtained by several sections of the Environmental Epidemiology Branch in support of epidemiologic research.

Major Contributions: The repository receives tens of thousands of samples annually and has processed them efficiently.

UNIVERSITY OF THE WEST INDIES (N01-CP3-1006-00)

Title: Epidemiology of HTLV-I in Jamaica

Current Annual Level: \$590,176

Person Years: 5

Objectives: To undertake in-depth surveys of HTLV-I in an endemic area.

Major Contribution: Studies of over 15,000 persons have provided a complete profile of the transmission and distribution of HTLV-I. Collection of data about the health risks of HTLV-I infection is in progress.

RESEARCH TRIANGLE INSTITUTE (N01-CP8-5649-00)

Title: Support Services for Retrovirus Epidemiology and Natural History in Hemophiliacs and Their Sexual Partners

Current Annual Level: \$500,000

Person Years: 8

Objectives: To support HIV natural history studies in hemophiliacs.

Major Contributions: The data from this project provide substantive information on the natural history of HIV infection from exposure to disease, including cancer.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05526-05 EEB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analytic Investigations of Selected Issues in Human Cancer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	LA. Brinton	Chief, Environmental Studies	EEB	NCI
Others:	K.P. Cantor	Epidemiologist	EEB	NCI
	G. Gridley	Statistician (Health)	EEB	NCI
	P. Hartge	Epidemiologist	EEB	NCI
	R.N. Hoover	Chief	EEB	NCI
	C. Schairer	Statistician (Health)	EEB	NCI
	M.H. Schiffman	Medical Epidemiologist	EEB	NCI

COOPERATING UNITS (if any)

Emory University (J. Liff), Fred Hutchinson Cancer Res Ctr (J. Daling), NJ State Dept Health (J. Schoenberg), Cetus Corp (M. Manos), Johns Hopkins (R. Kurman), Life Technologies (A. Lorincz), Kaiser Med Ctrs (W. Finkle, G. Friedman, A. Glass)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Environmental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

10.2

PROFESSIONAL:

8.2

OTHER:

2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The etiology of a variety of cancers has been pursued, oftentimes using multidisciplinary approaches. A major emphasis has been on investigating the etiology of female cancers, with substantial efforts expended on defining the role of the human papillomaviruses in several anogenital cancers (cervix, vulva, penis). Several natural history studies are underway which incorporate methodologic adjuncts to address problems inherent in many previous investigations. Also actively pursued has been the relationship of both endogenous and exogenous hormonal factors to several cancers. Of particular interest have been the effects of oral contraceptive use on the risk of premenopausal breast cancer and of combined estrogen/progestin therapy on cancers of the breast and endometrium. Attempts are also underway to assess risk factors for several relatively unstudied cancer sites, including cancers of the vagina, penis, and nasopharynx. Further efforts are being expended to clarify relationships of drinking water contaminants to a variety of cancers, pesticide exposures to risk of leukemia and non-Hodgkin's lymphoma, and therapy for rheumatoid arthritis to risk of subsequent hematopoietic cancers. A large study of multiple myeloma and cancers of the prostate, pancreas, and esophagus was completed and analyses are underway to assess reasons why these cancers occur more commonly in blacks than whites. Finally, analyses have been undertaken to examine the influence of gender and race on the incidence of cancers of the cervix, bladder, and lung.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

L.A. Brinton	Chief, Environmental Studies	EEB	NCI
C. Byrne	CEBTP Fellow	EEB	NCI
K.P. Cantor	Epidemiologist	EEB	NCI
Y. Chen	Visiting Fellow	EEB	NCI
G. Gridley	Statistician (Health)	EEB	NCI
P. Hartge	Epidemiologist	EEB	NCI
R. Herrero	Visiting Associate	EEB	NCI
A. Hildesheim	CEBTP Fellow	EEB	NCI
R.N. Hoover	Chief	EEB	NCI
N.A. Potischman	CEBTP Fellow	EEB	NCI
C. Schairer	Statistician (Health)	EEB	NCI
M.H. Schiffman	Medical Epidemiologist	EEB	NCI
S.R. Sturgeon	CEBTP Fellow	EEB	NCI
R.G. Ziegler	Epidemiologist	EEB	NCI

Objectives:

(1) To identify tumor sites for which there are a number of unusual demographic, laboratory or clinical associations indicating the necessity to evaluate a broad range of potential exposures. (2) To identify populations in which in-depth evaluations can be most efficiently carried out. (3) To design, conduct, and analyze these studies intensively.

Methods Employed:Investigations of Female Tumors

1. A population-based case-control study of breast cancer with an emphasis among women under the age of 45 years is underway in Atlanta, Seattle, and Trenton. Random digit dialing controls will be selected for all cases, and in Atlanta an additional control will be identified through a complex household survey, enabling the validity of these two methods of control selection to be compared. In Atlanta, the age range of study subjects has been expanded to age 54 to enable a fuller assessment of risk in relation to use of oral contraceptives, one of the main hypotheses to be addressed in the study. Also of interest in the study are dietary and anthropometric relationships (see project Z01CP05128-12 EEB). It is expected that approximately 2,000 women with newly diagnosed breast cancer and 3,000 controls will be recruited for study during a two-year period that began in May of 1990.

2. Data from the case-control study undertaken among participants in the Breast Cancer Detection Demonstration Project (involving 3,217 breast cancer cases, 3539 cases of benign breast disease, and 3545 normal screenees) were used to evaluate breast cancer risk associated with specific family history profiles, anthropometric changes, and mammographic densities.

3. The continuation of a follow-up study of a sample of participants in the Breast Cancer Detection Demonstration Project was completed in 1990. Questionnaires were obtained for 51,696 (86 per cent) of the study participants. A total of 798 breast cancers were reported during the continuation of the study. In addition, 293 colorectal, 286 endometrial, and 104 ovarian cancers were reported since the start of the follow-up study in 1979. Two percent (1,459) of the study subjects were deceased. Analyses are underway to examine the effects of menopausal hormones on the risk of breast and colorectal cancers as well as on all-cause mortality and mortality due to cardiovascular disease. Using mammograms available from the screening project, analyses are also in progress to assess the interactive effects of mammographic parenchymal patterns and family history of breast cancer on subsequent breast cancer risk. Analyses are also being conducted to determine the effect of specific factors on breast cancer prognosis.

4. A multidisciplinary study in five U.S. areas, involving 435 patients with endometrial cancer, 211 patients with hysterectomies for benign conditions, and 320 community controls, was completed and analyses are in progress. Although a major focus of the study is on dietary determinants (see project Z01CP05128-11 EEB), there is also the opportunity to examine data relevant to other suspected risk factors for this tumor, including exogenous hormones, alcohol consumption, and smoking.

5. A companion study of endometrial cancer in Shanghai, China, involving 268 cases and an equal number of population controls, was also completed and analyses initiated.

6. Data from a 1978-81 case-control study of 296 patients with primary epithelial ovarian cancer and 343 subjects admitted to Washington, D.C. area hospitals were used in a 12 study meta-analysis to assess risk associated with a variety of reproductive and medical factors. Various reports have been prepared for journal submission during this year.

7. A case-control study in Beijing, China of 112 epithelial ovarian cancer cases and 224 community controls enabled evaluation of risk in relation to a variety of reproductive, medical, familial, and lifestyle factors.

8. Data from a case-control study of 479 patients with invasive cervical cancer, 293 with in situ cancer and 789 community controls were analyzed to assess cancer risk in relation to a variety of suspect factors. The data were also examined in conjunction with Surveillance, Epidemiology and End Results (SEER) incidence data and data on prevalence of hysterectomy from the Cancer and Steroid Hormone Study to investigate the reasons for the higher rates of invasive squamous cell cervical cancer in blacks than whites in the U.S.

9. Data from a case-control study of invasive cervical cancer in four Latin American countries (Colombia, Costa Rica, Mexico, and Panama), involving interviews with 759 cases, 1,532 controls, and 689 husbands, were analyzed to assess risk in relation to injectable contraceptives, infectious agents, and nutritional factors (see project Z01CP05128-12 EEB).

10. A cross-sectional study of risk factors for cervical dysplasia was conducted in three hospitals in Washington, D.C. Women found to have abnormal Pap smears ($n = 326$) were compared to the remainder of the group with normal cytologic diagnoses. In total, 3,188 women were interviewed and cervical cell samples were taken at the time of Pap smear for human papillomavirus (HPV) testing. Currently, 700 samples are being tested for HPV, to assess the behavioral and demographic determinants of the infection.

11. A prospective study of HPV infection and subsequent cervical dysplasia is underway in an 18,000-woman cohort in the Kaiser Permanente, Portland prepaid health plan. For each woman, a cervicovaginal lavage has been frozen to permit a nested case-control study of incident dysplasia in relation to pre-morbid HPV type-specific infection. Those women excluded from the cohort at enrollment because of a baseline abnormal cytologic diagnosis are being compared to a random sample of the disease-free cohort in a prevalent case-control analysis.

12. A case-control study of cervical neoplasia and HPV infection has been initiated as part of a large screening project in Taiwan. A Pap smear, cervigram, short interview, and cervical swab for HPV testing will be obtained from a random population sample of 7000 women in two townships. Women with prevalent cervical neoplasia will be compared to controls in an attempt to determine why Taiwanese rates of cervical neoplasia are among the highest in the world.

13. A study of prevalent, incident, and recurrent cervical dysplasia was conducted in a private gynecologic practice in Washington, D.C. HPV testing and a 2-3 year follow-up were completed for 398 women.

14. The determinants of HPV infection in a Berkeley student health population were studied in 476 women obtaining routine Pap smears. The virus was assayed by polymerase chain reaction (PCR) gene amplification techniques, and risk factors for infection were assessed by self-administered questionnaires.

15. A study of the diagnostic reliability of cervical cytopathologic diagnoses has been initiated with collaborators at the Johns Hopkins Hospital Department of Pathology. Over 500 cytology and pathology slides are being reviewed by multiple cytopathologists to assess the reproducibility of the recently-introduced Bethesda system of cytologic diagnosis.

16. A case-control study in Chicago and upstate New York allowed assessment of risk factors for rarely occurring cancers of the vagina and vulva. Included for study were 209 vulvar cancer patients and 348 matched controls, and 41 vaginal cancer patients and 97 controls. These subjects were personally interviewed and had blood samples drawn for several infectious agent and micronutrient assays.

17. Data from a Swedish population-based cohort study of over 23,000 women prescribed non-contraceptive estrogens are being analyzed to assess the risk of breast cancer after estrogen and progestin replacement therapy. Exposure

information is available on all cases in the cohort diagnosed between 1977 and 1988 and a random sample of others in the cohort. Based on the distribution of estrogen and progestin exposure in the sample, observed to expected ratios for breast cancer in the total cohort are being calculated. This analysis updates a previous analysis which included cases diagnosed between 1977 and 1983. Data from this study were also analyzed to evaluate cause-specific mortality in relationship to type of hormone therapy.

18. A record linkage study is in progress in Denmark and Sweden to evaluate risk of selected cancers in relation to gynecologic operations. The large size of the study population (nearly 85,000 patients) will enable risk to be assessed in relation to various types of operations, including those that do and do not involve ovarian ablation.

19. A number of research projects have been undertaken in collaboration with three prepaid health plans. These include 1) evaluations of changes in incidence of breast cancer, malignant melanoma and squamous cell skin cancer over time in one health plan; 2) a small study of HPV infection and the risk of progression of low-grade cervical dysplasia, using PCR gene amplification techniques to type HPV infection in stored pathology specimens from women who later progressed to high-grade cervical neoplasia; and 3) a pilot study to determine the feasibility of a prospective cohort evaluation of a variety of exposures, particularly diet.

Other Investigations

20. To investigate reasons for the higher rates of four cancer types (multiple myeloma, prostatic, pancreatic and esophageal cancers) in blacks than whites, a population-based case-control study was conducted in three areas of the U.S. Personal interviews were completed on 587 myeloma, 1000 prostate, 527 pancreas and 900 esophagus cases and 2,153 controls. Information was collected on a variety of potential risk factors such as smoking and alcohol consumption, occupational history, lifestyle factors, usual adult diet, and medical conditions. A biochemical/laboratory component was included to examine the effects of hormones and nutrition on prostate cancer risk and to investigate the possibility of a genetic predisposition to multiple myeloma (HLA typing). Data are currently being analyzed to assess relationships of multiple myeloma to HLA types, prostate cancer to vasectomy, and pancreatic cancer to smoking and alcohol consumption.

21. A pilot project to assess the feasibility of conducting a full-scale case-control study of nasopharyngeal carcinoma in Taipei, Taiwan has been successfully completed. The full-scale study has recently been initiated. The goal of this 3-year study is to simultaneously assess genetic, infectious, dietary, and other lifestyle factors hypothesized to be linked to this cancer. Cases are being recruited from two large hospitals, where it is estimated that 60% of all NPC cases in the Taipei area are diagnosed. Each case is being matched with one community control as well as a subject with a biopsy for suspect NPC that is not confirmed. In addition to a detailed interview, blood, urine, and toe-nails are being sought. For cases and biopsy negative controls, biopsy samples are also being obtained, which will enable assessment

of p53 gene mutations. Attempts will be made to interview available mothers to assess early diet practices of study subjects. It is expected that approximately 425 cases, 400 biopsy negative controls, 425 community controls, and 380 mothers will be included for study.

22. A case-control study of leukemia and non-Hodgkin's lymphoma was conducted in Iowa and Minnesota. Interviews were conducted with 600 leukemia patients, 600 lymphoma patients, and 1,200 population-based controls. Information collected included occupational and medical history, farm-related exposures, exposure to ionizing radiation, solvents and pesticides, smoking, socio-economic status, and family history of cancer. Some findings have been published, and a manuscript on non-Hodgkin's lymphoma and farming will soon be released.

23. Data from a previously conducted bladder cancer study were analyzed to estimate the contribution of known risk factors to the male excess in risk. A previously conducted study of lung cancer is further providing the opportunity to evaluate reasons for the differing incidence of this cancer between blacks and whites.

24. The first phase of data collection for a case-control study of six cancer sites in Iowa, using a mail questionnaire, has recently been completed. There are between 375 and 685 cases from each case series (bladder, colon, rectum, pancreas, brain, and kidney), and 1,500 controls. The primary focus is on assessing the cancer risk associated with drinking water contaminants. Information was also collected on other risk factors, such as smoking, alcohol consumption, dietary patterns, weight, parity, and occupation. Data collection for the second phase, restricted to additional bladder cancer cases (900) and controls (900), is completed and data analysis of the combined study is in progress.

25. A case-control study of penile cancer in a high-risk area in the People's Republic of China was completed. A total of 141 cases and 150 community controls were recruited for interview and blood draw. In addition, 550 penile and cervicovaginal specimens were collected from cases, controls and wives of both types of subjects to permit an assessment of HPV transmission patterns and its role in the etiology of penile cancer. Blood samples have also been obtained to permit serologic studies of a variety of sexually transmitted agents.

26. A cohort of 12,000 patients with a hospital diagnosis of rheumatoid arthritis (RA) from 1965-1985 was identified in the Uppsala region of Sweden. These data were matched to the Swedish cancer registry, and cancer incidence among the patients compared to national rates.

27. A data base of 14 million hospital visits (5 million patients) to the more than 100 U.S. Veterans Administration (VA) hospitals (fiscal years 1970-1989) has been used to select cohorts and examine cancer risk (standardized incidence ratios) compared to internal (VA) and external (SEER) rates. Hospital charts and claim folders are obtained for some case-control comparisons, and to confirm diagnoses and procedures. Cohorts are also matched against the Social Security Administration (SSA) records and

Beneficiary Identification and Records Locator Subsystem (BIRLS) for mortality.

28. Patterns of mortality in a cohort of 10,000 aerial pesticide applicators identified from Federal Aviation Administration records were compared to 10,000 flight instructors and to U.S. white males. The cohort was followed through the end of 1979 to quantify the risk of traumatic death, and to evaluate chronic disease mortality in this group of pesticide-exposed workers. A second follow-up, through 1988, is in the data collection phase.

Major Findings:

Investigations of Female Tumors

Data from the BCDDP case-control study showed that obesity during childhood or adolescence was associated with reduced risks of both early and late onset breast cancer. Weight gain in adulthood, however, had a direct effect on later onset disease, particularly for larger invasive cancers, consistent with observations of poor breast cancer prognosis among obese women. Expanding on previous findings that parenchymal patterns are important predictors of subsequent breast cancer risk, analyses showed that the extent of breast density in conjunction with parenchymal patterns may provide further risk discrimination. Further analyses showed that a first degree family history of breast cancer was associated with a 2-fold increased risk and that the results from a mother's and sister's history were independent. Risk from a maternal history varied little by the subject's disease characteristics, but a sister's history appeared to relate to early onset and bilateral disease.

Preliminary analyses of ten years of follow-up of the BCDDP cohort show a reduction in risk of all-cause mortality associated with use of menopausal estrogens (RR=0.8, 95% CI 0.6-0.9). The reduction in risk appears limited to recent users, with no additional protection conferred by long-term usage. The decreased risk associated with use is restricted to women with low family incomes, suggesting that social class differences may account for part of the observed protection.

The endometrial cancer study in China, a population whose risk has not been substantially altered by use of exogenous estrogens, showed risk factors resembling those found in other studies. Elevated risks were associated with nulliparity, obesity and late ages at menopause, while long-term oral contraceptive use appeared to reduce risk.

In China, risk factors for ovarian cancer appear similar to those identified in high-incidence areas. Nulliparous women and/or those with histories of infertility were at elevated risk, while those with multiple pregnancies were at low risk. An excess risk was also found related to a history of longtime application of talc-containing dusting powder to the lower abdomen and perineum, although based on small numbers.

In the U.S. cervical cancer study, only minor differences between blacks and whites were found in the magnitude of risk factors. However, in line with the higher incidence rates in blacks, the prevalence of all major cervical cancer

risk factors, except cigarette smoking, was higher in blacks than whites. In this same study, invasive cervical cancer risk was reduced among users of barrier methods of contraceptives. This appeared to relate mainly to concomitant use of spermicidal agents, of note given their proven anti-viral capabilities. Risk factors for in situ cancer were generally similar to those identified for invasive cancer, with high risks relating to the reporting of multiple sexual partners, a history of an abnormal Pap smear or absence of screening, cigarette smoking, previous genital infections, and extended use of oral contraceptives.

In the Latin American cervical cancer study, there was evidence of increased risk associated with long-term use of injectable contraceptives. Data from this study also provided the first epidemiologic support for a significant interactive effect on risk of joint infection with HPV and the herpes simplex virus type 2 (HSV-2). Thus, women who tested positive only to HSV-2 were not at excess risk, those positive to HPV were at a 4-fold risk, and those positive to both HPV and HSV-2 were at a 7-fold risk. These results support previous clinical and laboratory speculation that these two viruses may act as cocarcinogens. In addition, the results are of interest in focusing further attention on the role of HSV-2 in the etiology of cervical cancer, since most epidemiologic studies have ignored its potential effects.

In the cohort study of HPV infection and cervical dysplasia, preliminary data from the first 21 incident cases and 63 matched controls suggest that HPV infection may precede and predict many cases of incident cervical dysplasia. Each woman had an HPV test while cytologically normal at enrollment, and again at the time of diagnosis of the incident case (for this group, on average 11 months later). According to a very sensitive polymerase chain reaction assay, 52% of the enrollment specimens from cases contained HPV DNA, compared to 16% of enrollment specimens from controls. At the time of diagnosis, 89% of repeat case specimens contained HPV, compared to 17% of controls, including 4 controls who were HPV-positive at both measurements. The results suggest that HPV positivity among cytologically normal women is associated with an increased risk of subsequent incident cervical dysplasia. HPV typing results are pending. A few hundred cases are expected over the next two years of follow-up.

During the enrollment phase of the same cohort study, over 700 cases of prevalent cervical dysplasia were identified. Five hundred of these cases were compared with a 500-woman random sample of the disease-free cohort. HPV DNA was detected by PCR in 17% of the control sample, in 80% of the low-grade cases and in 90% of the high-grade cases. The HPV typing results indicated that detection of HPV 16 or 18 was associated with a fortyfold increase in risk of prevalent low-grade dysplasia, and over a 100-fold risk of high-grade dysplasia. Univariate analyses showed current smoking, oral contraceptive use, and low socioeconomic status to be risk factors for dysplasia. Multivariate analyses will focus on the joint role of HPV and these other risk factors.

In the same population, the determinants of HPV positivity were investigated among the 500-woman sample of the disease-free cohort. On univariate analyses, increasing HPV prevalence was associated with decreasing age,

education level, and family income. In addition, prevalence was higher among unmarried women, oral contraceptive users, current smokers, and nulliparous women. There was also a strong decrease in HPV detection with increasing age among cases, suggesting the possibility of a cohort effect.

In the study of HPV infection in a Berkeley student health population, a lifetime history of multiple sexual partners was shown to be the strongest determinant of HPV positivity. Other independent risk factors included oral contraceptive use, black race, and age (prevalence decreased steadily with age).

Similar to cervical cancer, vaginal cancer risk was found to be elevated among women with low socioeconomic status and histories of genital warts. Sexual factors, however, did not appear to affect risk. More important were previous genital abnormalities, with significant associations seen for vaginal discharge or irritation, a previous abnormal Pap smear, or an early hysterectomy.

Analyses of cancer risk in the cohort of Swedish women treated with non-contraceptive estrogens showed a significantly increased risk of endometrial cancer, a slightly decreased risk of cervical cancer, and no increase in risk of cancers of the ovary, pancreas, large bowel, or kidney. The risk of liver or biliary tract cancers was significantly lower than expected, particularly in women who used potent estrogens, while the risk of breast cancer was slightly elevated. Risk of breast cancer increased with duration of estrogen treatment, reaching 1.7 after nine years. Although the numbers of women were small, the risk of breast cancer was highest among women who took estrogen and progestin in combination for extended periods. Analyses of cause-specific mortality showed that among 19 main categories of death, risk estimates were generally below unity, suggesting that healthier women take estrogens.

Other Investigations

Initial findings from the study of cancers common in blacks suggest that black and white males with the HLA CW2 antigen may be at increased risk for multiple myeloma.

Analysis of data from the leukemia and non-Hodgkin's lymphoma (NHL) study in Iowa and Minnesota suggested a relationship of use with several insecticides, especially with first use at least 20 years prior to diagnosis. Insecticides associated with elevated non-Hodgkin's lymphoma risk among farmers included several chlorinated hydrocarbons and organophosphates.

Findings from the multi-site case-control study in Iowa indicated that parous women are at lower risk of bladder cancer than nulliparous women. This is possibly due to hormonal changes associated with pregnancy, and may be related to the lower risk of bladder cancer among females.

Analyses of the national bladder cancer data showed that, even in the absence of exposure to cigarettes, occupational hazards, or urinary tract infections, males had a persistent excess disease risk. Possible explanations for the excessive risk in men include environmental and dietary exposures not yet

identified and innate sexual characteristics such as anatomic differences, urination habits, or hormonal factors.

In the penile cancer study, a major risk factor was the presence of phimosis or paraphimosis, particularly when so severe that circumcision was used for treatment. A relationship of risk with poor personal hygiene, premarital or extramarital sexual relations, and prior genital diseases (including warts) was also noted, suggesting an etiologic role for sexually transmitted agents, including HPV.

The Swedish rheumatoid arthritis (RA) patients had no overall excess of cancer incidence. There were expected excesses of hematopoietic cancers, particularly lymphomas and CLL, and unexpected deficits of several sites (stomach, bladder, colorectal, liver, and breast).

The Veterans Administration data provided information on prostate cancer associated with transurethral prostatectomy, and hospital diagnoses for a drug abusers study. Computer analyses of rheumatoid arthritis, infectious mononucleosis, splenectomy, and vasectomy cohorts are being expanded to include the extra four years of data. Three studies are still in the process of obtaining hospital charts (Klinefelters, rheumatoid arthritis, infectious mononucleosis). An acromegaly study was completed (computer analyses and hospital chart review), which showed an excess of digestive cancers.

A historical cohort study of aerial pesticide applicators and flight instructors, with follow-up through 1979, showed a dramatically high risk of death due to traumatic injury, with risk among applicators being about 1.8 that of instructors. Among cancer sites, leukemia was statistically elevated among applicators as compared to instructors. Several other sites showed small, non-significant risk elevations, but the follow-up period was short and is now being extended.

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CONTRACTS IN SUPPORT OF THIS PROJECT

WESTAT, INC. (N01-CP6-1078)Title: Continuation of Follow-up on Participants in the Breast Cancer Detection Demonstration ProjectCurrent Annual Level: \$190,000Person Years: 2.5

Objectives: The main objectives of this project are to evaluate through a prospective study design such risk factors for breast cancer incidence as exogenous hormone therapy, smoking, alcohol consumption, and diet; to determine etiologic factors for other cancers, such as lung, endometrial, ovarian and colorectal cancers; and to examine the effects of exogenous hormones on mortality from heart disease, and hospitalization for fractures, gallbladder disease, and diabetes.

Methods: This contract allows continued follow-up of a cohort of approximately 61,000 women who had previously participated, between 1973 and 1980, in a breast cancer screening program, the Breast Cancer Detection Demonstration Project. A self-administered mailed interview was sent to participants in 1988-1989. Operative and pathology reports were collected for all breast procedures and newly diagnosed cancers reported on the mailed questionnaire. Death certificates were requested for all subjects determined to be deceased.

Major Contributions: Completed questionnaires were obtained for 51,696 (86 percent) of the 60,079 eligible participants. Questionnaires were not obtained for the 1,708 participants (2 percent) who were deceased, 505 (1 percent) who were too ill to be interviewed, 1,459 (2 percent) who refused, 2,746 participants (5 percent) who could not be contacted by the end of the follow-up period, and 1,963 participants (3 percent) who could not be traced. All questionnaires have been coded, keyed, and machine edited. Death certificates were received for 1,469 of 1,708 participants (86 percent) known to be deceased and medical records were obtained for 5,107 of 5,640 (90 percent) eligible breast procedures.

Work has begun at NCI on analysis of the data. Pathology reports are being matched to self-reported cancers and data files prepared to assess the relationship of exogenous hormone use to morbidity from cancers of the breast and colon and to mortality from all causes.

WESTAT, INC. (N01-CP9-5605)

Title: Breast Cancer in Women Under the Age of 45 Years: Coordinating Center

Current Annual Level: \$204,243

Person Years: 1

Objectives: This contractor serves as a coordinating center for the case-control study of breast cancer among younger women, which is being conducted in Atlanta, Seattle, and Trenton.

Methods: The contractor developed all data collection forms for the study, as well as the associated manuals. In addition, they standardly trained the data abstractors, interviewers, and study supervisors. They are also performing random digit dialing to identify a population-based control series for the study. Eight separate telephone screening waves have thus far been performed, with the response rate to the telephone screener ranging from 88-90% across all sites. The contractor has also been responsible for monitoring the course of the study at all sites, deriving solutions to potential response problems and assuring maintenance to a standardized protocol.

Major Contributions: Data collection is currently in progress, with the study being at approximately its mid-point.

ANNUAL REPORT OF

THE RADIATION EPIDEMIOLOGY BRANCH EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM DIVISION OF CANCER ETIOLOGY NATIONAL CANCER INSTITUTE

October 1, 1990 through September 30, 1991

Formed in February 1984, the Radiation Epidemiology Branch attempts to identify and quantify the risk of cancer in populations exposed to ionizing radiation, alone or in combination with cytotoxic drugs. Whenever possible, experimental findings are integrated with epidemiologic observations. This past year Dr. Zdenek Hrubec, Branch Expert in Biostatistics retired, and Dr. Elaine Ron, Epidemiologist, left the Branch to join the National Academy of Sciences as a Research Associate at the Radiation Effects Research Foundation. Dr. Dana Friedman joined the Branch as an Epidemiology and Biostatistics Fellow, after obtaining her doctoral degree from New York University. Maria Klebanoff also joined the Branch as a Public Health Analyst. The Branch attracts visiting scientists from a number of countries for relatively short periods of intense collaboration. This past year, visiting scientists have come from England, Czechoslovakia, Israel, Germany, Japan, Sweden, Yugoslavia, Denmark, Finland, Canada and the People's Republic of China. Several research activities continued to generate a great deal of public and Congressional interest, notably Branch studies of cancer risk around nuclear facilities, lung cancer and indoor radon, and childhood leukemia and electromagnetic field radiation.

RESEARCH PROGRAM:

Human populations exposed to ionizing radiation are being studied to improve the estimates of radiation risk, especially at low doses, and to evaluate the influence of host and environmental factors on radiogenic cancer risk. Such data are needed to base regulatory and other decisions about the potential hazard from medical, occupational, and environmental exposures, and to assess the value of exposure avoidance as a means of cancer prevention. Basic mechanisms of cancer causation are being studied with biochemical approaches.

Medical Exposure Studies: The study of medically exposed populations has proven to be a valuable means for quantifying late radiation effects. Doses to various organs can usually be estimated accurately, nonexposed patients are often available for comparison, information on other risk factors can frequently be obtained, and medical facilities often follow patients for long periods of time after treatment. Patient populations given high-dose, partial body, therapeutic irradiation provide the only evidence that some cancers, e.g., the rectum, can be induced by ionizing radiation. Scattered radiation from such exposures result in relatively low doses to surrounding tissues. Patients given multiple, low-dose, diagnostic radiologic procedures also provide an accurate source of information on potential cancer risk following long-term fractionated or protracted exposures.

Tuberculosis patients given multiple chest fluoroscopies during pneumothorax treatment of tuberculosis between 1930-1954 were recently re-surveyed in Massachusetts. The risk of radiogenic breast cancer remained high even 50 years after exposure occurred. Moreover, repeated, relatively low radiation doses were determined to pose a future risk of breast cancer that was similar to that seen

following acute exposures of the same total dose, the risk appears cumulative, adolescence is an especially sensitive age, and women over 40 years of age at exposure were at little or no risk. A small sample of women who developed breast cancer at an early age is being evaluated for the presence of defective p53 tumor suppressor genes in circulating blood lymphocytes to address the possibility of a heritable susceptibility to radiogenic breast cancer. A record-linkage study of tuberculosis patients in Connecticut, matching rosters with records in the Connecticut Tumor Registry, found a high risk of breast cancer among women who received multiple chest fluoroscopies prior to age 30.

Studies of children treated for retinoblastoma are continuing. Radiotherapy greatly increased the risk of deaths due to osteosarcoma among children with bilateral, but not unilateral, retinoblastoma, confirming the important interaction between genetic susceptibility and radiation exposure. Detailed dosimetry has been performed to estimate radiation doses to individual organs or tissues in other studies of childhood cancer. High-dose radiotherapy was linked to an increased risk of thyroid cancer, even at doses as high as 60 Gy (6,000 rad).

A number of studies provide information on the effect that age at exposure might have on subsequent cancer risk as well as the patterns of risk over time. Follow-up of 10,000 Israeli children irradiated for ringworm of the scalp, and 16,000 matched comparison subjects has been completed. A fourfold increase in skin cancer of the head and neck, primarily basal cell cancer, was observed. Malignant melanoma was not significantly elevated. A cell survival assay was used to look for DNA repair defects in skin fibroblasts. There was a suggestion of a slightly higher sensitivity to radiation damage at the cellular level among patients with skin cancer. Frequent fluoroscopic examination of the chest for monitoring tuberculosis treatment was linked to a dose-related excess of basal cell skin cancers. In collaboration with investigators at Michael Reese Hospital, organ doses were computed for over 4,000 persons irradiated for benign conditions of the head and neck. Medical records were abstracted so that the method of tumor detection could be ascertained. A telephone interview study to elicit information on new tumor incidence is in progress.

A twofold risk of breast cancer was previously reported in a study of women diagnosed with scoliosis during childhood. The data were suggestive of an association with diagnostic x-ray exposure during adolescence, but the number of observed cases was small. An additional 5,000 women from 12 different institutions across the country were recruited for study. Risks will be evaluated with regard to critical biological stages when breast tissue may be more sensitive to the carcinogenic action of ionizing radiation, such as puberty or menarche. Women with scoliosis who developed breast cancer following excessive x-rays are being evaluated for the presence of mutated p53 genes in circulating lymphocytes.

The risk of leukemia, lymphoma, and multiple myeloma in relation to diagnostic x-ray procedures was evaluated in a case-control study conducted within two prepaid health plans. The findings confirm that diagnostic x-ray procedures are unlikely to be a major cause of leukemia, lymphoma, or multiple myeloma in our society. The time-related patterns suggested that observed associations were non-causal, with large numbers of x-rays being prompted by a variety of pre-diagnosis symptoms. However, women who received very large numbers of x-rays were at high risk for multiple myeloma.

To learn whether radiotherapy might increase the risk of second breast cancer, case-control studies of long-term survivors of breast cancer are nearing completion in Connecticut and Denmark. Women treated after age 40 are of special interest because there is, to date, little evidence that radiogenic breast cancers occur among such women. Collaborative studies in Sweden revealed that radioactive iodine (^{131}I) did not increase the risk of leukemia. These findings suggest that the carcinogenic potential of beta particles from internal iodine-131 might be lower than that of brief doses of external x-rays or gamma rays. An excess of stomach cancer, however, was suggested among patients given very high doses. Ongoing studies include patients given diagnostic doses of radioactive iodine in Yugoslavia and Israel. A subsequent study of ^{131}I in Sweden was initiated this year to ascertain more accurately thyroid nodular disease through neck examinations.

A survey of 36,000 patients treated for hyperthyroidism, primarily Graves disease, in the United States is nearing completion. Treatment occurred between 1946 and 1964 at one of 19 medical centers. Cancer mortality among those treated with radioactive iodine will be compared to that among those treated with surgery and/or drugs. Analyses will examine risks by ^{131}I dose (based on amount administered and percent uptake by the thyroid), as well as age at exposure.

Radioactive Thorotrast given during cerebral angiography was linked to a high risk of liver cancer and leukemia among Danish epileptics. An increase in lung cancer was also noted, which might be due to continuous exhalation of the thoron gas that is a byproduct from the decay of Thorotrast. Studies of lung tissue are planned to evaluate the presence of a mutated tumor suppressor gene p53 and a mutated oncogene K-ras in tumor and adjacent healthy tissue. Thorotrast-exposed populations in Sweden, Portugal, and the United States are being considered for possible study of the late effects from continuous exposure to alpha particles among very long-term survivors.

A recently completed study of cancer mortality among 4,483 women irradiated for benign gynecologic disorders (BGD) in Massachusetts or Rhode Island was supplemented with 8,470 additional women treated for BGD at hospitals in New York or Connecticut. A comparison group consists of 3,185 non-irradiated women. Analysis of the combined data will examine associations between cancer risk and radiation dose, radiation modality, age at irradiation and time since irradiation. Follow-up of the study population is being extended from 1984 through 1989.

Together with investigators in Uppsala, Sweden and at Kaiser-Permanente in Portland, Oregon, a case-referent study of thyroid cancer and adenoma in relation to history of exposure to diagnostic x-rays was initiated. Exposure histories will be ascertained by review of radiology records. Characteristics of the two medical care systems make it possible to obtain nearly complete x-ray histories. In addition, recently-diagnosed cases and matched reference subjects will be interviewed by telephone and asked to recall their x-ray histories. Accuracy of recall and the possible effect of recall bias on radiation risk estimates will be assessed.

Radiotherapy for peptic ulcer appears to be related to increased deaths from non-Hodgkin's lymphoma and cancers of the stomach, pancreas, and lung. Mortality was determined for 2,000 irradiated patients and 2,000 comparison patients. Dose-response analyses are in progress, and the possible interaction between surgery, radiotherapy, and type of ulcer is being evaluated with regard to risk of stomach cancer.

Prenatal x-ray exposure was associated with an increased risk of childhood cancer in a case-control study of twins identified through the Swedish Twin Registry. The observed relative risks were consistent with previous studies, suggesting that the developing fetus may be more sensitive to ionizing radiation than are children irradiated just after birth. However, the findings were not statistically significant and cohort comparisons with cancer rates from primarily single-born children did not reveal a cancer excess despite the much greater x-ray exposure of twins *in utero*.

A study of leukemia following treatment for breast cancer involving four U.S. registries was completed. Record linkage identified 90 cases of secondary leukemia and preleukemia among breast cancer patients. A detailed case-control study compared the treatment history between cases and 264 matched breast cancer controls. Average bone marrow doses of 7.2 Gy (720 rad) were associated with a twofold risk of acute nonlymphocytic leukemia. The highest risk was associated with marrow exposures of more than 10 Gy (1000 rad). There was also a suggestion that chemotherapy with alkylating agents might interact in a multiplicative fashion to increase the risk of leukemia.

Several other analytic studies continue. An international study is evaluating the risk of leukemia among women treated for uterine corpus cancer to quantify the dose-response relationship following partial-body therapeutic radiation. Ten population-based registries are included. Preliminary results indicate that patients treated with radiotherapy have a significantly increased twofold risk of developing leukemia, except the chronic lymphocytic cell type. The dose-response relationship will be modeled and compared to previous studies of cervical cancer. The risk of second cancers is also being evaluated in over 100,000 patients with endometrial cancer to select cancer sites for further analytic and dosimetric study. Similarly, the risk of second cancers among long-term survivors of cervical cancer is being investigated to determine cancer sites for future dose-response studies. Studies of over 2,000 women receiving radiation to the pituitary gland and ovaries as treatment for infertility in New York and Israel are nearing completion. A feasibility study of patients given neutron therapy at M.D. Anderson Hospital and Cleveland Clinic was completed. Preliminary findings are essentially negative, reflecting perhaps the fact that neutron exposure to small volumes of tissue results more in cell-killing, than cell transformation. An essential component of the program of epidemiologic studies of medically-irradiated populations is accurate dosimetry for specific organs. A team of medical physicists at the M.D. Anderson Hospital continued to work with the Branch in this regard.

Atomic Bomb Survivor Studies: The Branch collaborates with the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan, on a program of epidemiological and multidisciplinary studies of the lifespan study (LSS) sample of 94,000 A-bomb survivors, plus 26,000 nonexposed residents of the two cities. This cohort is possibly the single most valuable source of epidemiological information on radiation carcinogenesis in humans.

In a new follow-up study involving 840 incident breast cancer cases, women exposed as children or teenagers were at greatest risk and women over age 40 at the time of the bombings were at least risk. A case-control interview study was conducted to investigate breast cancer risk factors and their possible interaction. Parity, age at first delivery, number of children, and lactation history were found to be strongly related to risk, whereas age at menarche and age at menopause were not. Reproductive factors appear to interact multiplicatively with radiation dose;

additivity can be effectively ruled out. The high risk of radiation-related breast cancer among women exposed at young ages may arise because such exposures tended to occur before the first pregnancy. A pathology review of breast tissue obtained at autopsy from women without clinical breast cancer found significant associations between radiation dose and both proliferative and non-proliferative disease, suggesting that in women over 40 when exposed, many radiation-related lesions may not have developed into cancers because promotion by hormonal stimulation was lacking.

A binational pathology review of lung tissue samples from the studies of A-bomb survivors and U.S. uranium miners was conducted to evaluate radiation-induced lung cancer risk, especially as related to age, time after exposure and smoking history. Results suggest that apparent cell type differences are explainable in terms of the probability of radiation causation and smoking history. There do not appear to be cell types that are uniquely caused by inhaled alpha emitters or external gamma rays.

In a study of colorectal cancer, colon cancer incidence was strongly related to radiation dose, whereas rectal cancer risk was unrelated to dose. Colon cancer risk did not vary significantly by subsite, relative to baseline rates. Excess relative risk was inversely related to age at exposure.

Assays of stored serum samples were carried out for cancer cases diagnosed subsequent to blood drawing and for matched controls. There was evidence of lower iron levels among persons who later developed stomach cancer, and a weak association between breast cancer and free estrogen. A new incidence study of non-Hodgkin's lymphoma involves the collaboration of epidemiologists, statisticians, and hematopathologists, employing immunohistochemical assays and the polymerase chain reaction to obtain refined diagnoses. Other new studies include an assay of the mutation spectra of the p53 tumor suppressor gene in lung tissue from A-bomb survivors and mustard gas workers in collaboration with NCI's Laboratory of Human Carcinogenesis. Incidence studies of salivary gland, thyroid gland, and skin cancers have been initiated.

Occupational and Environmental Exposure Studies: Long-term exposure to radiation in occupational and environmental settings are being conducted to provide more accurate estimates of cancer risk, especially at relatively low levels.

Cancer mortality is being evaluated among 145,000 certified x-ray technologists. Radiation exposure levels are being characterized for over 90,000 long questionnaire respondents based on year work began, total number of years employed, types of x-ray procedures performed, and personal diagnostic and therapeutic radiation exposures experienced. Computer linkage with the records of the nation's largest commercial dosimetry company has provided at least partial exposure histories on over 85,000 technologists. Additionally, specific exposure information was obtained for persons who developed leukemia, and cancers of the breast, thyroid, and lung, by contacting their employers directly. Dosimetry data were similarly obtained for a random sample of the entire cohort. Case-control studies will compare exposures among controls matched to cases on the basis of age, sex, year of registry enrollment, and survival. Preliminary mortality analyses suggest an increase in breast cancer but not lung cancer or leukemia. A second survey will be initiated to obtain detailed information on cancer incidence, and to evaluate whether preconception radiation might be related to childhood leukemia in offspring.

A study of diagnostic x-ray workers in China revealed a 21% greater incidence of cancer than expected, based on the experience of physicians who did not routinely use x-rays. Leukemia was significantly increased overall, and risk was higher for x-ray workers who began employment before 1970, when exposures probably were greater than in more recent years. A pilot study was developed to explore the feasibility of using recently developed mutational assays to estimate, retrospectively, cumulative radiation doses for a sample of individual workers. If doses can be estimated with confidence, then valuable information might be obtained about cancer risks associated with continuous or repeated exposure to low-dose radiation.

Following a successful pilot study, negotiations were completed with the nation's largest commercial dosimetry company to provide annual cumulative dose data for our ongoing study of radiologic technologists and to establish a dosimetry registry of approximately 250,000 radiation workers receiving dosimetry services from this company in 1978 and later. Mortality studies using such a dosimetry registry of radiation workers are facilitated by the availability of key identifiers and the ability to link with the National Death Index, which began in 1979. In addition, negotiations were completed with the Nuclear Regulatory Commission to create a comprehensive registry of radiation workers, notably nuclear power workers in the United States.

Neutron exposures to 191 well loggers at four oil fields in China were measured over a three month period using CR-39 polycarbonate dosimeters. Cumulative neutron exposures were below the minimum detectable level of 0.02 mGy (2 mrad) for most workers. Doses were slightly lower than literature values for well loggers in North America, possibly because of differences in drilling activity. Because doses are so low, an epidemiologic study of cancer among Chinese well loggers is unlikely to be informative about the carcinogenicity of neutrons relative to sparsely ionizing radiation.

Collaborative studies of indoor radon exposures among women were completed in New Jersey, Sweden and China. Results from the New Jersey investigation were difficult to interpret because of inordinately low exposure levels and very low response rates. In Chinese dwellings, no increase in risk was found with exposure to relatively high concentrations of radon gas. The Swedish data suggested a radon risk but are also difficult to interpret because adjustment for occupancy appreciably lowered the estimated risk. Analyses of these data sets in parallel have begun to examine more fully the risk of lung cancer possibly associated with residential radon. A study in Missouri continues with 600 lung cancer cases to be evaluated. A methodologic evaluation was completed which determined that applying CR-39 film to household items made of glass, such as picture frames owned for long periods of time, provides a means to estimate cumulative radon exposure over the age of the items.

The study of the occurrence of cancer in counties that have or are close to nuclear facilities was completed and the results published. Included were 62 nuclear electric generating plants that went into operation by 1981, and ten other facilities that engaged in isotope preparation and separation, production of enriched uranium and plutonium, manufacture of weapons components and other activities involving radioactive materials. Sixteen forms of cancer were studied at the level of mortality and, for four facilities for which it was possible, cancer incidence. Taken as a whole, cancer risks were slightly higher before the facilities began to operate than afterwards, and there was no evidence that leukemia

or other cancers, in children or at any age, were increased as a consequence of the operations of any of the nuclear facilities.

A study to assess the association between childhood acute lymphocytic leukemia (ALL) and low frequency electromagnetic field (EMF) exposures continued. The study will utilize a subset of 600 case-control pairs from an investigation by the Children's Cancer Study Group (CCSG). A detailed assessment of electric appliance use will be made, and EMF and radon measurements will be collected. External transmission wires will be diagramed. Pilot studies have been completed which suggest that between-child variation in total EMF exposure is adequately predicted using residential exposure measurements alone, indicating that measurements in daycare centers or schools will not be necessary. Questionnaire data are being collected on potential confounding factors such as pesticides and prenatal x-rays.

Medicinal Exposures: The purpose of this project is to evaluate the carcinogenic potential of medical treatment with drugs. Populations under study include cancer patients reported to population-based cancer registries (especially the SEER Program), persons treated at major institutions, and those treated in randomized clinical trials.

A case-control study of leukemia following breast cancer was completed. A total of 90 leukemia cases and 264 matched breast cancer controls were evaluated in four U.S. registries. Patients treated with alkylating agents were at high risk of leukemia that differed by the type of drug administered. Significant dose-response relationships were established for several alkylating agents; risk was notably elevated for patients treated with both radiation and alkylating agents.

The Branch continued its efforts to screen the SEER registry database for increased risks of therapy-related second cancers. The most recent review found that chemotherapy increased the risk of leukemia following small cell lung cancer, cancers of the breast, ovary and testes, and Hodgkin's disease, non-Hodgkin's lymphoma, and multiple myeloma. The risk of endometrial cancer following breast cancer is being evaluated to detect possible increased risks following hormonal therapy (i.e., tamoxifen).

Anticonvulsive drugs were not found to be transplacental carcinogens in a study of the offspring of Danish epileptic women exposed to phenobarbital and other anticonvulsive drugs.

Multiple Primary Cancer Studies: The Branch has a continuing interest in the etiology of multiple primary cancers, in particular tumor constellations that are associated with late treatment effects, genetic predisposition, endocrine and dietary factors, and environmental exposures. Data from the SEER Program and other population-based cancer registries have been used to examine second cancer risks among patients with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and cancers of the breast, uterine corpus and cervix.

Laboratory Studies: New biochemical measures of radiation dose are being incorporated into epidemiologic studies of irradiated populations. In collaboration with the Lawrence Livermore National Laboratory, the glycophorin-A mutational assay (GPA) and chromosome translocation analyses using *in situ* hybridization with chromosome-specific fluorescent polynucleotide probes (chromosome painting) will be applied to workers at the Sellafield nuclear reprocessing plant in England and

correlated with measured cumulative doses. Results will also be compared with classical cytogenetic evaluations.

High-dose pelvic irradiation appears to be associated with a reduced risk of breast cancer, even if the irradiation occurs after menopause. Data suggest that irradiation of the adrenal glands, as well as the ovaries, might influence breast cancer risk. To explore further the possible role of ovarian and adrenal hormones, estradiol, estrone, androstenedione and testosterone levels were measured among 206 cervical cancer patients at intervals of 2, 5, 10, and 15 years post-treatment. Pre-treatment and 6-month post-treatment samples also have been measured for recently diagnosed cases. Hormone levels will be examined in relation to radiotherapy, ovarian and menopausal status, time since treatment, and age.

Cultured skin fibroblasts from two irradiated populations were analyzed at the Brookhaven National Laboratories. *In vitro* survival assays were conducted looking for evidence of DNA repair defects at the cellular level among persons who have developed radiation-induced cancers. Populations studied include the atomic bomb survivors with and without breast cancer, and Israeli patients irradiated for ringworm of the scalp with and without cancer of the thyroid or skin. A study was completed among atomic bomb survivors of the relationship between cancer induction and levels of hormones and micronutrients in sera obtained prior to cancer diagnosis. Immunohistochemical and polymerase chain reaction techniques are being applied to stored tissue from lymphoma cases among A-bomb survivors to obtain refined diagnoses. The presence of germline defects in the p53 tumor suppressor gene is being sought in three populations of women at high risk of radiogenic breast cancer.

Methodologic Studies: Methods are being investigated for increasing the information yield of existing bodies of data and for treating analytic problems that arise during the course of other studies. Working in collaboration with the original investigators, attempts are made to resolve apparent inconsistencies among different studies and to strengthen inferences, by reanalyzing the basic data in parallel, using identical stratifications with respect to age at exposure, length of follow-up, and identical assumptions with respect to dose-response models and latent period. This approach is being applied to several sets of breast cancer incidence data and thyroid cancer incidence data from different exposed populations. Three data sets of lung cancer and indoor radon are being analyzed, and data sets of lung cancer among underground miners are being collected.

Consideration of statistical power, sample size, and dose-response model assumptions have been explored as part of a continuing review of special problems of estimating cancer risk from low-dose exposures to ionizing radiation. Breast cancer risk among A-bomb survivors has been evaluated by explicitly modeling the temporal distributions of baseline and excess risk. A new statistical approach was developed to analyze interaction between radiation dose and other risk factors in nested case-control studies incorporating matching of cases and controls on radiation dose. Development of a package of epidemiologic programs for personal computers is nearing completion. Several of these programs were used by the National Academy of Sciences BEIR V committee as the primary tool for the analysis of data from a wide variety of studies of radiation effects.

Workshops: A workshop of the collaborators of the study of second cancers following uterine corpus cancer was held to discuss planning for the cohort analysis and radiation dosimetry. A start-up meeting was held with collaborators on the study of

thyroid neoplasia following exposure to diagnostic radiation. Much of the effort was directed to the design of the telephone interview form to be used to record recalled histories of diagnostic x-ray and nuclear medicine procedures.

Reviews: The Branch provides comprehensive and critical reviews of the health effects of ionizing radiation. Such reviews include a comprehensive survey of cancers following exposure to ionizing radiation, cancer and nuclear energy, thyroid cancer and radiation, cancer from naturally occurring radiation, the influence of host factor susceptibility on radiogenic risk, bone cancer and radiation, an evaluation of the statistical and epidemiologic issues concerning estimation of cancer risk from low doses of ionizing radiation, and overviews on the importance of latent period, risk projection and time-response models in estimating cancer risks. These critical reviews help the Branch stay current in the area of radiation carcinogenesis and suggest new directions for the research programs.

OTHER ACTIVITIES:

Branch members continue to advise and collaborate with other agencies and individuals involved in radiation research and regulatory activities, such as the National Council on Radiation Protection and Measurements, the Department of Energy, the Oak Ridge Associated Universities, the Environmental Protection Agency, the DHHS Subcommittee to Coordinate Federal Radiation Activities, the National Aeronautics and Space Administration, the International Commission on Radiation Protection, the Commission of the European Communities, the International Agency for Research on Cancer, and the World Health Organization, among others. Staff have also met with scientists in Europe and the Soviet Union to discuss possible studies of populations exposed to radiation from the Chernobyl nuclear reactor accident. At times, Branch members have become heavily involved in controversial public policy issues and debates, most recently with the issue of possible cancer risk associated with low-frequency electromagnetic field radiation.

The Branch continues to support development of and access to state and national databases for use in long-term follow-up studies. Record systems successfully accessed to date include Social Security Mortality, Health Care Financing Administration, U.S. Postal Service, Department of Veterans Affairs, National Death Index, state vital statistics bureaus, credit bureaus, and motor vehicle department files. Internal Revenue Service records have been accessed for occupational studies conducted in collaboration with the National Institute for Occupational Safety and Health. Additionally, the Branch continues to identify resources that will facilitate studies of populations exposed to radiation. In this regard, Branch efforts have been successful in assisting the Nuclear Regulatory Commission in the development of a registry of radiation workers to further epidemiologic research in the area of occupational exposure to radiation. Additionally, major databases available through commercial location firms were evaluated for their usefulness for epidemiologic studies, including a nationwide vehicle identification number file and a pension benefit file that derives information from five different sources (Social Security Administration, Federal Civil Service, Department of Defense, Railroad Retirement Board, and California death tapes).

Collaborative record-linkage studies have continued to utilize more fully resources that are available in cancer registries in the United States and other countries. The Branch also provides on-the-job training of staff at the postdoctoral level, supervises graduate students during NIH summer training programs, provides field research opportunities for doctoral candidates at schools of public health, and

collaborates with visiting scientists from a number of countries, including Canada, Denmark, England, Finland, Germany, Japan, Sweden, Israel, Yugoslavia, Czechoslovakia and the People's Republic of China.

Ongoing research projects and new directions for research are critically reviewed. Oversight and evaluation are provided through weekly Branch meetings; monthly meetings with support services groups; frequent contact with other support services and collaborating groups; several working groups (e.g., A-bomb survivor studies and drug studies); interagency committees; formal review mechanisms for the careful scrutiny of questionnaires and protocols by internal and external review committees; *ad hoc* external review groups for major studies (e.g., the study of Childhood Leukemia and Electromagnetic Field and Radon Exposure); and a variety of advisory bodies that oversee Institute activities, notably the Board of Scientific Counselors of the Division of Cancer Etiology.

SUMMARY REPORT
RADIATION EPIDEMIOLOGY BRANCH
PROGRESS ON RESEARCH CONTRACTS

Thirteen research contracts, discussed below, were active in FY91.

Cancer in the Opposite Breast Following Radiotherapy for Primary Breast Cancer. Radiotherapy for breast cancer is being evaluated as a possible risk factor for second primary breast cancer occurring in the contralateral breast. The dependence of risk on dose and age at exposure will be evaluated. Study subjects were drawn from approximately 50,000 women with breast cancer reported to the population-based tumor registry in Denmark between 1943-1975. Cases are all women with breast cancer who developed a second primary breast cancer eight or more years after treatment for the first malignancy. Controls are women with a primary breast cancer who did not develop a second primary breast cancer. One control has been matched to each case based on age at initial breast cancer diagnosis, calendar year of diagnosis, and survival time. Approximately 1,000 cases and 1,000 controls are available for study. Individual dosimetry determinations are nearly complete. Record abstraction is nearing completion. A no cost extension for this contract was granted. Preliminary analyses have begun.

Thyroid Cancer Risk Following Diagnostic and Therapeutic 131-I Exposure. The risk of thyroid cancer and other cancers following diagnostic 131-I exposure is being evaluated. Populations from Yugoslavia and Israel are being studied to more powerfully evaluate risks following childhood exposures. Approximately 25,000 patients exposed between 1963-1979 were identified at the Nuclear Medicine Institute in Slovenia, Yugoslavia and 31,000 patients examined between 1955-1979 were identified at Beilinson Hospital in Israel. Radiation and clinical data are being abstracted from the nuclear medicine and hospital records. By computer linking the study cohorts to population-based cancer and death registries, malignant tumors will be identified. Expected numbers of cancers will be computed based on age-, sex-, site-, and calendar-time-specific incidence data from the cancer registries. Record abstraction is nearing completion and tracing and linkage procedures have been tested.

Thyroid Nodularity Following Exposure to Diagnostic 131-I. In Sweden, a selected sample of 1,000 women who were included in an earlier record-linkage study of diagnostic 131-I are to be asked to come to a clinic, complete a brief questionnaire concerning their medical history, and have their thyroid glands examined by palpation. Certain hormonal and immunologic assays will be performed for women with palpably abnormal thyroids and a 10% sample of other women. The population will include a comparison group of 250 women coming to the clinic for routine mammographic screening. Although the previous record-linkage study of 35,000 persons did not find a statistically significant excess of thyroid cancer, a more sensitive method for ascertaining outcomes, such as palpating the former patients' thyroids, will yield more definitive results.

Epidemiologic Studies of Cancer among A-bomb Survivors. Investigations based on a cohort of 94,000 A-bomb survivors and 26,000 nonexposed individuals are carried out at the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki,

Japan. Collaboration is facilitated by personnel exchanges between RERF and NCI. Emphasis is placed on site-specific studies of cancer incidence, as determined from death certificates, tumor and tissue registries, searches of hospital and clinical records, and on case-control interview studies in which epidemiologic factors other than radiation, as determined from existing records or by interview, are investigated. Multidisciplinary approaches include reviews of diagnostic material by panels of pathologists, biochemical probes of stored tissue specimens, and assays of stored blood sera obtained prior to cancer diagnosis.

The number of identified incident female breast cancer cases increased from 564 by 1980 to 824 by 1985; the number of bilateral cases increased from 10 to 17, and seven male cases were identified. In the breast cancer case-control study, protective effects were seen for parity, number of children, early age at first delivery, and total length of lactation. Interaction analyses tend to indicate synergistic relationships between certain risk factors and radiation dose. For women exposed to similar radiation doses at similar ages, the likelihood of subsequent breast cancer was more than twice as high if no pregnancy had occurred by the time of exposure than for parous women. Regardless of reproductive status at the time of exposure, radiation-induced breast cancer was less likely among women who experienced their first deliveries at young ages, had many children, or had lengthy lactation histories. A manuscript on the methodology of a nested case-control study of breast cancer, with matching on radiation dose, has been published in the RERF Commentary and Review series, and submitted for journal publication. Manuscripts based on analyses of main effects for factors other than radiation dose, and of interactions of these factors with radiation dose, have been submitted for internal review at NCI and RERF.

A manuscript submitted for publication summarizes findings of a study of colorectal cancer incidence. Colon cancer risk was strongly related to radiation dose, but rectal cancer risk was not elevated. Interview data from a separate case-control study confirmed that high exercise levels are associated with reduced colon cancer. Dietary history data are being analyzed. In the hormonal and nutrient-assay studies, it appeared that low ferritin levels were associated with subsequent stomach cancer risk; this may possibly be linked to undetected internal bleeding (Cancer, in press). No relationship was observed for lung cancer. A suggestive difference was observed between breast cancer cases and controls with respect to free estrogen levels among women who were postmenopausal at the time of blood drawing. In the pathology comparisons of lung cancer materials from A-bomb survivors and Colorado uranium miners, variations in cell type appeared to be explained in terms of radiation dose and smoking history. In both populations, small cell cancer was relatively more frequent, and adenocarcinoma relatively less frequent, among cases with high radiation dose, whereas the relative frequency of squamous cell carcinoma was apparently related only to smoking history. A manuscript has been prepared and submitted for internal review at NCI and RERF. Also, data are being analyzed for a case-control interview study of thyroid cancer.

Diagnostic X-rays, Prior Medical Conditions, Prescription Drug Use, and Other Factors and Risk of Leukemia, Lymphoma, and Multiple Myeloma. A manuscript describing the risk of hematopoietic malignancies following diagnostic x-ray exposure among members of two Kaiser-Permanente health plans was published in the Journal of the American Medical Association. No radiation association was found for chronic lymphocytic leukemia, one of the few cancers never linked to radiation. For the other leukemia patients, a dose-response relationship was suggested when all diagnostic x-rays were considered. However, none of the dose-response trends were

significant and the risk dropped to near normal when x-rays within five years of diagnosis were excluded from the analysis, suggesting that many of the x-rays may have been given for early symptoms of the disease itself. Patients with non-Hodgkin's lymphoma cases were x-rayed slightly more often than controls; however, this association disappeared when recent x-ray exposures were excluded. This pattern suggests that the x-rays were administered for conditions arising during the early phases of lymphoma development. Overall, multiple myeloma patients did not receive significantly more x-ray exposure than controls; however, all of the dose-response trends approached statistical significance. The most heavily exposed were at significant risk regardless of the exposure-lagging intervals. Analyses of prior medical conditions, use of prescription drugs, and other factors are currently underway.

Diagnostic X-rays and Risk of Thyroid Cancer and Adenoma. Case-referent studies of the relationship, if any, between exposure to diagnostic radiation and the development of thyroid neoplasia are being conducted in Uppsala, Sweden (500 cases, 500 reference subjects) and among members of the Kaiser-Permanente (Northwest) Medical Plan (75 cases, 75 reference subjects). Exposure histories will be ascertained by reviewing medical and radiology records. Characteristics of the two medical care systems make it likely that nearly complete medical histories can be obtained. In addition, recently diagnosed cases and matched reference subjects will be asked to recall their x-ray histories. Accuracy of recall and the possible effect of recall bias on radiation risk estimates will be assessed.

Second Cancers Following Radiotherapy for Uterine Corpus Cancer. Increased risks of second cancers (other than leukemia) related to radiotherapy are being identified in a cohort study of over 100,000 patients with uterine corpus cancer. Data is being obtained from 13 cancer registries, including the nine SEER registries, and registries located in Ontario, Canada, Denmark, Finland and Sweden using the record-linkage Master Agreement mechanism. Observed and expected numbers of second primary cancers will be tabulated by type of treatment, age and year of uterine corpus cancer diagnosis, time since treatment, histologic type of cancer, and race. Person-years at risk analyses will be conducted for each strata. Data will be sent to NCI for a combined analysis of data from the 13 registries. The cohort study will explore the risks of radiation-induced cancer by time since first exposure and age at first exposure. An important goal of this study is to determine whether specific second cancer sites should be pursued in detailed case-control studies in which the dose-response relationship will be quantified. Individual registry analyses are nearing completion and a combined analysis is ongoing.

Biodosimetry for Long-term Exposure to Low-levels of Ionizing Radiation. To estimate cumulative radiation exposures from long-term, low-level occupational exposures at a nuclear fuel facility, the NCI, in collaboration with Lawrence Livermore National Laboratory, is applying two recently developed methods of biodosimetry. These are the glycophorin-A somatic mutation assay (GPA) and chromosome painting using fluorescent *in situ* hybridization for translocation analysis (FISHTA). Workers to be evaluated have all received cumulative doses of more than 0.5 Gy (50 rad) from multiple low-dose exposures of gamma radiation over the past 20 to 30 years. The frequency of mutations and translocations in these workers will be correlated with actual recorded doses from personal dosimeters to evaluate whether GPA and FISHTA are reliable estimators of exposure. These techniques will also be applied to a control group of non-exposed workers. Additionally, classical cytogenetics will be carried out as another method of comparison with FISHTA. Other populations with documented excesses of leukemia to

be evaluated include Chinese medical x-ray workers and women irradiated for benign gynecologic disorders. This interagency agreement with the Department of Energy will be for three years and commenced in the second half of FY91.

RADIATION EPIDEMIOLOGY BRANCH
RESEARCH CONTRACTS ACTIVE DURING FY 91

<u>Institution/Principal Investigator/ Contract Number</u>	<u>Title</u>
Danish Cancer Registry Hans H. Storm N01-CP-85639-01	Second Cancer Following Treatment for Uterine Corpus Cancer
Danish Cancer Registry Hans H. Storm N01-CP-51057	Cancer in the Opposite Breast Following Radiotherapy for Primary Breast Cancer
Finnish Cancer Registry Eero Pukkala N01-CP-85638-01	Second Cancer Following Treatment for Uterine Corpus Cancer
Israel Cancer Registry Leah Katz N01-CP-85635-01	Record-Linkage Study of Patients Exposed to Diagnostic Radioactive Iodine
Kaiser Foundation Research Institute Andrew Glass N01-CP-95648-01	Diagnostic X-rays and Risk of Thyroid Cancer and Adenoma
Karolinska Institute Lars-Erik Holm N01-CP-15652	Thyroid Nodularity Following Exposure to Diagnostic 131-I
Lawrence Livermore National Laboratory Ronald H. Jensen Y01-CP-10561	Biodosimetry for Long-term Exposures to Low Levels of Ionizing Radiation
National Academy of Sciences Charles Eddington N01-CP-71128	Epidemiologic Studies of Cancer Among A-bomb Survivors
Ontario Cancer Treatment Foundation Eric J. Holowaty N01-CP-85625-01	Second Cancer Following Treatment for Uterine Corpus Cancer
Slovenia Cancer Registry Vera Pompe Kirn N01-CP-85634-01	Record-Linkage Study of Patients Exposed to Diagnostic Radioactive Iodine
Swedish Cancer Registry Hans-Olov Adami N01-CP-85636-01	Second Cancer Following Treatment for Uterine Corpus Cancer
Swedish Cancer Registry Hans-Olov Adami N01-CP-85636-03	Diagnostic X-rays and Risk of Thyroid Cancer and Adenoma

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01CP04481-15 REB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Studies of Radiation-Induced Cancer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J.D. Boice, Jr. Chief REB NCI

Others: C.E. Land Health Statistician REB NCI
S. Jablon Expert Statistician REB NCI
R.A. Kleinerman Epidemiologist REB NCI
R.E. Curtis Statistician REB NCI
P. Inskip Staff Fellow REB NCI
L. Travis Pathologist REB NCI

COOPERATING UNITS (if any)

Radiation Effects Research Foundation, Japan (D. Preston); Michael Reese Hospital (A. Schneider); University of Minnesota (J. Mandel); Karolinska Institute (L.-E. Holm); Harvard University (R. Monson)

LAB/BRANCH

Radiation Epidemiology Branch

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

11.0

PROFESSIONAL:

8.0

OTHER:

3.0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The risk of cancer in populations exposed to ionizing radiation is evaluated among Japanese A-bomb survivors, patients given therapeutic or diagnostic radiation, occupational groups, and persons exposed to naturally occurring radiations. Biochemical approaches are incorporated into studies to help define basic mechanisms. Program members serve on committees advising the government and international agencies.

Results of studies suggest that (1) indoor exposure to radon may be less risky than previously believed; (2) diagnostic x-ray exposure is unlikely to be a significant cause of leukemia or lymphoma in our society, although excessive exposure may increase the risk of multiple myeloma; (3) living near nuclear facilities in the United States is not associated with a detectable increased risk of childhood leukemia or any other cancer; (4) the risk of radiation-induced breast cancer declines with increasing age at exposure, the dose response is linear, and risk remains for at least 50 years; (5) exposure prior to first pregnancy carries a higher breast cancer risk than exposure afterwards; (6) radiotherapy for breast cancer increases the risk of leukemia, especially in combination with alkylating agents; (7) low-dose radiotherapy to treat uterine bleeding induces many more leukemias than high-dose radiotherapy to treat cervical cancer or uterine cancer; (8) high-dose radioactive iodine treatments did not increase the risk of leukemia, suggesting that protraction of dose reduces risk; (9) high-dose radiotherapy in childhood increases the risk of thyroid cancer; (10) radiotherapy for bilateral retinoblastoma greatly increases the risk of osteosarcoma, indicating the importance of a genetic susceptibility in radiation risk.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

John D. Boice, Jr.	Chief	REB	NCI
Charles E. Land	Health Statistician	REB	NCI
Gilbert W. Beebe	Health Statistician	CEB	NCI
Ruth A. Kleinerman	Epidemiologist	REB	NCI
Seymour Jablon	Expert Statistician	REB	NCI
Zdenek Hrubec	Expert Statistician	REB	NCI
Lois B. Travis	Pathologist	REB	NCI
Rochelle E. Curtis	Statistician	REB	NCI
Katherine W. Chen	Computer Programmer	REB	NCI
Michele M. Morin	Epidemiologist	REB	NCI
Peter D. Inskip	Staff Fellow	REB	NCI
Dana Friedman	Epidemiology Fellow	REB	NCI
William J. Blot	Chief	BB,DCE	NCI
Linda M. Pottern	Epidemiologist	EEB	NCI
Martha Linet	Epidemiologist	BB,DCE	NCI
Jay Lubin	Biostatistician	BB,DCE	NCI
Robert Tarone	Biostatistician	BB,DCE	NCI
Michael Alavanja	Epidemiologist	EBP	NCI
Margaret A. Tucker	Chief, Family Studies Section	EEB	NCI
Frederick P. Li	Chief, Clinical Studies Section	CEB	NCI

Objectives:

(1) To plan and conduct independent and cooperative epidemiologic research to identify and quantify the risk of cancer in populations exposed to ionizing radiation (e.g., x-rays) and nonionizing radiation (e.g., ultraviolet light). Populations with documented therapeutic, diagnostic, occupational, environmental or military exposures are studied; (2) to characterize the risk of radiation-induced cancer in terms of tissues at risk, dose response, radiation quality, fractionation of dose, time after exposure, sex, age at exposure and at observation, and possible modifying influences of other environmental and host factors; (3) to develop statistical and epidemiologic methodologies to facilitate epidemiologic research and to explore and formulate models of radiation carcinogenesis that may help define basic mechanisms of cancer induction, including the integration of experimental findings with epidemiologic observations; (4) to conduct case control and follow-up (cohort) studies of cancer risk in patient populations given diagnostic or therapeutic radiation alone or in combination with cytotoxic drugs and other forms of treatment; (5) to conduct population studies to examine possible analogs of radiation carcinogenesis in man, such as the induction of cytogenetic abnormalities in circulating lymphocytes, and to integrate laboratory markers of radiation exposure and tissue response into epidemiologic studies designed to clarify the patterns of cancer risk and the mechanisms of action; and (6) to advise and collaborate with other agencies and individuals involved in radiation research and regulatory activities.

Methods Employed:

Populations exposed to ionizing radiation are studied to strengthen the quantitative basis for risk estimation, especially at low doses, to improve understanding of the role of host and environmental factors on radiogenic cancer risk, and to provide insights into carcinogenic mechanisms. Approaches to biochemical epidemiology have been expanded this year, and controversial topics continue to be tackled, such as cancer risk associated with indoor radon, living near nuclear facilities, and exposure to low-frequency electromagnetic field radiation.

A. Medical Exposures. Populations exposed to medical irradiation are valuable for quantifying late effects because (1) organ doses can usually be accurately estimated, (2) nonexposed patients are often available for comparison, (3) information on other risk factors can frequently be obtained from existing records, and (4) medical facilities often follow patients for long periods of time after treatment. The only evidence that a cancer can be induced by ionizing radiation for relatively insensitive tissues comes from patient populations given high-dose, partial-body, therapeutic irradiation. For other sites, the best evidence of low-dose risk comes from populations given multiple, low-dose, diagnostic irradiation resulting in high cumulative exposures. The radiation studies program strives to assure that maximum benefit is derived from existing epidemiologic resources, and attempts to initiate studies of populations not previously evaluated, but which offer unusual potential for new information. Over 20 medically irradiated populations are currently under study: women irradiated for cervical cancer, uterine corpus cancer, benign gynecologic disorders, infertility, or breast cancer; adults irradiated for non-Hodgkin's lymphoma or peptic ulcer; children irradiated for lymphoid hyperplasia, retinoblastoma and other cancers, or tinea capitis; patients who received diagnostic radiographic procedures for tuberculosis or scoliosis; twins who received prenatal x-ray; leukemia, lymphoma, multiple myeloma, and thyroid cancer patients who received prior diagnostic x-ray examinations; hyperthyroid and other patients treated with radioactive iodine; and patients given diagnostic doses of radioactive iodine, Thorotrast for cerebral angiography, or radium to treat bone disease.

Populations receiving therapeutic irradiation are described below.

1. Studies of childhood irradiation continue. The possibility of detecting and clarifying increased cancer risk in children due to radiation therapy is enhanced by the minimal confounding effect of other carcinogenic influences, such as smoking or occupation, the possible greater susceptibility of young people to environmental carcinogens, and the potentially long period of life available after successful treatment. Studies include children irradiated for enlarged tonsils in Boston and Chicago, tinea capitis in Israel, and retinoblastoma in New York and Boston. Blood studies included the evaluation of serum calcium levels and plasma thyroglobulin concentrations. Chromosome aberrations in circulating lymphocytes were also investigated to evaluate the effect of radiation in causing long-term damage in somatic cells from partial-body exposures for tonsil and thymic irradiations.

2. The tumorigenic effects of low to moderate doses of radiation have been studied extensively in a population of young adults who received radiation treatment for tinea capitis during childhood. This retrospective cohort study is comprised of 11,000 irradiated subjects; 11,000 disease-free, nonirradiated, matched comparison subjects chosen from the general population; and 5,400 disease-free, nonirradiated sibling comparisons. Repeated dosimetric studies were conducted to measure individual site-specific organ doses. Cancer incidence was determined using the National Cancer Registry and the records from the pathology departments of the 22 major hospitals in Israel. Mortality was ascertained by computer linkage with the Central Population Registry. Cause of death was obtained from the Death Register. To evaluate the possibility that the high relative risk of radiogenic thyroid and skin cancer might be due to enhanced host sensitivity to DNA damage, a biochemical epidemiology study was conducted. To evaluate further skin cancer risk factors, a study including a dermatologic examination also was completed. Indicators of skin color as proxy measures of sun sensitivity, as well as self-reported sun exposure and tanning experience, were studied.
3. Over 9,000 persons who survived at least 2 years after a diagnosis of childhood cancer in 13 hospitals in the United States and other countries were studied for the risk of second cancer development. Analyses are being completed of data from cases and matched controls to quantify the risks associated with radiation or chemotherapy treatments. Collaborative dosimetry support is being provided for a similar investigation conducted in the United Kingdom.
4. Cancer risk is being evaluated in relation to organ dose among women treated for benign gynecologic disorders (BGD) in Massachusetts, Rhode Island, Connecticut, and New York during the 1920s to 1960s. The study population includes 9,768 women irradiated by intrauterine radium or external beam x-rays and a comparison group of 3,185 nonirradiated BGD patients. Doses were in the tens of Gy to the uterus, 1-15 Gy to adjacent organs, and tenths of Gy to several Gy to active bone marrow and organs in the abdomen. Post-treatment survival of BGD patients was high, and the population provides an opportunity to address late effects of radiation exposure. The frequency of chromosome aberrations among surviving BGD patients also was examined.
5. A study of leukemia following treatment for breast cancer involving four U.S. registries was completed. Record linkage identified 90 cases of secondary leukemia and preleukemia among breast cancer patients. A detailed case-control study compared the treatment history between cases and 264 matched breast cancer controls.
6. Cancer mortality following radiotherapy for peptic ulcer is currently being analyzed. About 2,000 patients who were exposed between 1937-1965 have had organ doses reconstructed. The dose to the stomach was 15 Gy. Their mortality is being compared with 2,000 patients treated by surgical or medical means. Dose-response analyses are in progress, and

interaction of stomach cancer risk with type of surgery and ulcer is being investigated.

7. Studies on the carcinogenic effects of radiation therapy for infertility have continued. A mortality study is being carried out on a cohort of approximately 900 women treated by one radiologist in New York City between 1925 and 1960, and cancer incidence is being evaluated in a cohort of about 1,300 women treated in Israel. Organ doses have been calculated. The ovary and uterus received approximately 80 cGy (80 rad), and the active bone marrow about 16 cGy (16 rad). To evaluate genetic damage, a feasibility study is planned to obtain and store bloods from a sample of subjects, their husbands, and their biologic children.
8. Evaluating the tumorigenic effects of neutrons in humans is important not only for assessing risks to patients exposed clinically, but also for estimating risk to persons exposed occupationally. A feasibility study of over 500 cancer patients receiving neutron therapy was completed at M.D. Anderson Hospital in Houston, Texas and Cleveland Clinic Foundation in Ohio. Radiation organ doses were calculated for a sample of exposure situations. Results from the feasibility study will be used to decide whether an international study including over 2,000 two-year survivors treated in neutron therapy centers in the United States, Europe and Japan should be initiated.
9. An international study is evaluating the risk of second primary cancers among women treated for cancer of the uterine corpus cancer to quantify the dose-response relationship following partial-body therapeutic radiation. Ten population-based registries are included. The study of leukemia focused on 203 leukemia cases following uterine corpus cancer and 730 uterine corpus cancer controls. The dose-response relationship will be modeled and compared to previous studies of cervical cancer. Other second cancer sites that should be pursued in future detailed case-control studies are being identified.
10. A collaborative study has continued to address some of the methodologic problems associated with an investigation of over 5,000 persons irradiated for enlarged tonsils and other benign conditions of the head and neck at Michael Reese Hospital. Clinical and radiation therapy records were abstracted and organ doses estimated. The study population was redefined to be more homogeneous in terms of treatment and age. A telephone questionnaire was developed, and a follow-up survey is in progress.
11. An analysis of second cancers in patients treated for non-Hodgkin's lymphoma (NHL) was conducted using data available from SEER registries. Cancer risk was evaluated in relation to radiotherapy and chemotherapy in 29,000 patients diagnosed with NHL between 1973 and 1987 in one of nine areas participating in the SEER Program. Histopathologic material was obtained for 11 of 14 patients in the SEER Program in whom Hodgkin's disease was reported following NHL. This sequence of diagnoses is uncommon, and in view of the difficulties inherent in the classification

of lymphomas, it was felt that all pertinent materials should be reviewed in collaboration with the NCI Laboratory of Pathology.

12. Two international studies evaluating the risk of second primary cancers were initiated through the record linkage mechanism. Long-term survivors of cervical cancer and non-Hodgkin's lymphoma are being evaluated. Second cancer sites that might be pursued in future detailed case-control studies will be identified.

Populations receiving diagnostic irradiation are described below.

13. Twins are especially suitable for studies of prenatal x-ray exposures because it used to be common practice to examine twin pregnancies by x-ray. This results in a relatively high fraction of x-rayed subjects and also reduces possible confounding due to medical indications for the procedure or accessibility of medical care. Registries of more than 32,000 twin births in Connecticut and 100,000 births in Sweden were used to evaluate cancer occurrence among the twins through linkage with population-based cancer registries. Evaluation of risks of x-ray exposure, determined from a review of obstetrical and pediatric records, is of particular interest. However, the research also serves to document the overall cancer experience of twins, which for unexplained reasons appears to be lower than that of the single born.
14. Tuberculosis patients who received multiple chest fluoroscopies during pneumothorax treatment of tuberculosis between 1930 and 1954 are continually being followed to evaluate the patterns of risk among long-term survivors. Attempts are made to quantify these risks and to describe the duration of latency periods, changes of risk with time after treatment, age of the subject at the start of treatment, and age at the time of observation. Cancers of the breast, lung, esophagus, thyroid and leukemia are of particular interest. Patients were initially treated at sanatoria in Massachusetts and Connecticut prior to 1954. A new questionnaire was developed to obtain cancer information on long-term survivors. Women who developed breast cancer at a young age are being examined for evidence of a mutation in the p53 tumor suppressor gene in circulating blood lymphocytes. This biochemical component will provide information on a possible interaction between a genetic susceptibility and radiation exposure to increase cancer risk.
15. A case-control study to evaluate the risk of specified hematopoietic malignancies following diagnostic x-rays was completed and a manuscript published. Adult cases of leukemia, lymphoma, and multiple myeloma diagnosed between 1956-1982 in Portland, Oregon and Oakland, California were matched to controls within the same health plan, by sex, age and year of health plan entry, and number of years as a plan member. The types and number of x-ray procedures experienced were abstracted from medical records, and each procedure was classified and assigned a probable bone marrow dose.

16. Case-referent studies of the relationship, if any, between thyroid cancer and exposure to diagnostic radiation were initiated among residents of the Uppsala (Sweden) Health Care Region and members of the Kaiser-Permanente (Northwest) Medical Plan. Radiology and medical records will be reviewed to ascertain histories of exposure to x-rays and nuclear medicine procedures. In addition, recently diagnosed cases and matched reference subjects will be interviewed by telephone and asked to recall their diagnostic radiation histories. Accuracy of recall and the possible effect of recall bias on radiation risk estimates will be assessed.
17. A nearly twofold excess risk of breast cancer associated with diagnostic x-rays was found in a pilot study of about 1,000 women with scoliosis. To quantify the risks of radiation-induced breast cancer at an age of apparent high sensitivity and for which little data exist, this study was expanded to include an additional 4,600 women. Because of the intense x-ray monitoring of patients with scoliosis that occurs around puberty, it will be possible to examine radiation risks with respect to age at exposure, stage of breast development, and menarche. Patients have been enrolled from ten large orthopedic medical centers, and cancer incidence and mortality are being determined from death certificates, medical records, and questionnaires. A biochemical component to evaluate mutated p53 tumor suppressor genes in blood lymphocytes is being considered to evaluate the role, if any, this gene might have in radiation-induced breast cancer.

Populations receiving isotopes are described below.

18. The carcinogenic risks associated with exposure to diagnostic and therapeutic levels of radioactive iodine are being evaluated in the United States, Sweden, Israel, and Yugoslavia. This is a topic of considerable public health interest in light of the widespread use of radioactive iodine in medicine and its presence in fallout from nuclear weapons tests and releases from nuclear power reactors. There is considerable controversy over the effectiveness of radioactive iodine in inducing malignancies relative to that of external x-rays or gamma rays. Cohorts of approximately 25,000 and 31,000 patients exposed to diagnostic ¹³¹I in Slovenia and Israel, respectively, were assembled. The rosters of exposed patients will be linked to population-based registries to ascertain vital status and cancer incidence. Record abstraction is nearing completion and tracing and computer linkage procedures were tested.
19. An evaluation of the risk of thyroid nodularity and cancer among patients exposed to low-dose radioactive iodine in Sweden began. A sample of 1,000 women who were included in an earlier record-linkage study of diagnostic ¹³¹I will be asked to come in to a clinic, complete a brief questionnaire concerning their medical history, and have their thyroids palpated. Women who received either very high or very low exposures to diagnostic ¹³¹I, and who were of young age (<20y) at the time of exposure will be selectively enrolled. A group of 250 women from the

general population undergoing routine mammographic screening will be included for comparison. In addition, a newly developed mutational assay (glycophorin-A) will be evaluated to learn more about biological markers as potential dosimeters.

20. Nine hundred West German patients injected with radium 224 during the late 1940s for benign bone disease are being followed for late effects. Information on reproductive history, medication, and other variables is being sought by mail questionnaire to clarify apparent excesses of breast, liver, and kidney cancers. Experimental and theoretical dosimetry models for these organs are also being investigated through collaboration with radiobiologists.
21. The late carcinogenic effects of radioactive Thorotrast are being evaluated among patients given this contrast agent during cerebral angiography. Danish epileptics are currently under study in collaboration with the Armed Forces Institute of Pathology, where re-cut materials from paraffin blocks of hepatic tumors were examined for the presence of Thorotrast using energy dispersive x-ray analysis. Additional populations of Thorotrast-exposed subjects in Denmark, Sweden, Portugal and Massachusetts are being pursued to quantify late effects of alpha particle exposures among long-term survivors. Lung tissue from patients with lung cancer is being evaluated with respect to mutations in p53 and K-ras genes.

Other projects are intended to strengthen inferences from studies of medically irradiated populations in general.

22. Dosimetry: An essential part of the program of epidemiologic studies of medically-irradiated populations is an accurate estimation of radiation doses to specific organs. A team of medical physicists works with the Branch on dosimetry problems using physical measurements on patients, anthropomorphic phantoms, and a Monte Carlo computer code developed in collaboration with the Oak Ridge National Laboratory and the Center for Devices and Radiological Health, Food and Drug Administration. Radiation dose estimates for specific organs have been obtained for tuberculosis patients repeatedly exposed to fluoroscopic x-rays; persons irradiated for treatment of peptic ulcer; patients with cervical cancer, endometrial cancer or benign gynecological disorders treated with intracavitary radium and external beam x-rays or gamma rays; children irradiated for enlarged tonsils or thymus gland, tinea capitis, or retinoblastoma and other cancers; persons with leukemia, lymphoma or multiple myeloma who received diagnostic x-rays; persons exposed to multiple diagnostic x-rays for monitoring the progression of scoliosis; and women treated with radiation for breast cancer who subsequently developed a second breast cancer. Determinations are ongoing for women irradiated for infertility; cancer patients treated with neutrons; and x-ray technologists.
23. Biochemical and cytogenetic studies: New biodosimetry techniques are being applied to a population of occupationally exposed workers at a nuclear processing plant at Sellafield, U.K., in conjunction with the

Lawrence Livermore National Laboratory and include the glycophorin-A mutational assay and translocation analysis using *in situ* hybridization with chromosome-specific fluorescent polynucleotide probes (chromosome painting). A multiple end-point analysis of these two techniques and classical cytogenetic findings and actual recorded doses should provide information on the utility of these two new techniques to estimate radiation doses accumulated at low levels over many years.

The usefulness of classical cytogenetics as a biological dosimeter in persons with partial-body irradiation was also explored in six medically-irradiated populations in collaboration with cytogeneticists at Oak Ridge Associated Universities. Populations that have been investigated include cervical cancer patients, tuberculosis patients, persons exposed as infants for enlarged tonsils or thymic glands. Other populations currently under study are women irradiated for benign gynecologic disease, and cancer patients treated with neutrons. *In vitro* neutron curves have been generated and will be used to interpret the *in vivo* findings. A cell survival assay was used to look for DNA repair defects at the cellular level among atomic bomb survivors and persons irradiated for tinea capitis.

Heritable mutations in the p53 tumor suppressor gene are being evaluated in two populations at high risk for radiogenic breast cancer: tuberculosis patients given multiple chest x-ray fluoroscopies and scoliosis patients excessively exposed to spinal x-rays during puberty. Mutations in p53 and the K-ras oncogene are also being evaluated in several populations demonstrating excessive lung cancers: individuals given Thorotrast, patients with non-Hodgkin's lymphoma, and persons exposed to excessive amounts of radon.

A reduced risk of breast cancer has been observed among cervical cancer patients who were irradiated postmenopausally as well as among those irradiated premenopausally. Serum estrogen and androgen levels were measured to evaluate the possible importance of ovarian and adrenal irradiation in contributing to the lowered risk for irradiated and nonirradiated cervical cancer patients (total, 206 women) at intervals of 2, 5, 10, and 15 years post-treatment, and pretreatment and 6-month post-treatment for recently diagnosed cases. Data will be analyzed in conjunction with samples collected previously for intervals 20 and more years post-treatment.

B. Atomic Bomb Survivors. Since 1979, the Branch has been collaborating with the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan, on a program of epidemiological studies of atomic bomb survivors. Studies are based on a defined cohort of 94,000 A-bomb survivors, most with individual radiation dosimetry, and another 26,000 nonexposed residents of the two cities and a clinical subsample, originally numbering 20,000, which has been solicited for biennial medical examinations since 1958 and for which there are extensive clinical records and stored biological specimens. There are also community-based tumor and tissue registries and an autopsy and pathology program. The collaborative program emphasizes site-

specific incidence studies, interview studies, and multi-disciplinary investigations using stored biological materials.

1. A major effort is being made to improve the coverage by the RERF tumor registry of hospitals and clinics within Hiroshima and Nagasaki and their environs. This involves sending teams of medical students, working part-time under the supervision of registry staff, to examine the records of institutions that have not been covered regularly, and employing temporary staff to work for periods of a year or more in other institutions that have large collections of cases.
2. Person and person-year denominators for the proper evaluation of incidence data from the RERF tumor registry, registries elsewhere in Japan, and other sources of cases are being obtained by matching the Life Span Study rosters of registered A-bomb survivors, administered by the Ministry of Health and Welfare through local city and prefecture offices for health insurance and compensation purposes. Secondary sources include mail surveys and information requests to the family registries of individual cohort members.
3. Current studies of cancer incidence are focused on the colon (1950-80), female breast, malignant lymphoma, skin, salivary glands, and thyroid gland. The lymphoma study will include all cancers of lymphoid derivation, including lymphocytic leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma (NHL). The emphasis in this study will be on the re-classification of all NHL utilizing the modified Working Formulation. In addition, immunophenotyping of NHL into B-cell and T-cell types will be undertaken, and polymerase chain reaction (PCR) methodology will be employed to identify HTLV-I in cases of adult T-cell leukemia/lymphoma. Point mutations in K-ras and N-ras oncogenes will also be characterized.
4. Cancers of the female breast (1950-80 to be followed by interviews of new cases and controls through 1985), colon and rectum (1950-80), and thyroid gland are included in ongoing case-control interview studies. The emphasis of the breast cancer studies is on reproductive factors and their interaction with radiation dose, while diet, exercise, and occupational history are focuses of the colon cancer study. Thyroid cancer is known to be caused by radiation exposure, whereas little is known about other factors; diet and reproductive history are of major interest for the current study which involves a large component of nonexposed, non-cohort cases.
5. Hormonal and nutrient assays have been performed using stored serum samples, obtained from cases and controls well before diagnosis of breast, endometrium, thyroid, lung, and stomach cancer. Hypotheses of interest include increased risk of breast and endometrial cancer among women with above-normal levels of non-protein-bound estrogen, and the roles of retinol, selenium, and zinc, and iron as risk modifiers for lung and stomach cancer.

childhood acute lymphocytic leukemia (ALL). The Children's Cancer Study Group (CCSG) is evaluating a broad variety of risk factors in telephone interviews with parents of 2,000 newly diagnosed ALL cases and random-digit-dial controls. The NCI component involves assessing the EMF and radon exposures of 600 cases from six states and their matched CCSG controls. Based on the pilot study, a decision was made to obtain normal and low power spot measurements and a 24-hour measurement of the EMF fields in each child's current home and all previous homes lived in for a period of six months or more after conception, within five years of diagnosis. Wire coding information will also be collected. Nonresidential exposures, including those occurring at schools and daycare centers, will not be measured, unless further pilot testing contradicts earlier results that suggest that most of the variability in children's EMF exposures is derived from residential exposures. A measurement of the local geomagnetic field strength will be made in each residence that is assessed for EMF, and an alpha track radon detector will be placed in each of these homes for one year. The mother of each child will be interviewed in person to collect information on her use of electrical appliances during pregnancy and the child's use of appliances. Information on exposures to potentially important confounding factors, such as pesticides, benzene and medical x-rays also will be collected.

5. Follow-up of a cohort of 27,011 Chinese diagnostic x-ray workers and a comparison group of 25,782 other medical specialists was extended by five years, from 1980 to 1985. A study of the feasibility of using recently developed mutational assays to estimate, retrospectively, radiation doses to individual workers is planned.
6. The increased occurrence of cancers, especially leukemia, in areas around certain nuclear facilities was reported by several studies in the United Kingdom. A survey around 62 nuclear facilities in the United States was conducted to determine whether such excesses occurred in this country also. Included in the study were 52 nuclear electric generating stations and ten other facilities that engage in fuel reprocessing, produce or fabricate plutonium, or do other work with radioactive materials. Cancer mortality and, when possible, cancer incidence in counties that include or are near such facilities were compared with cancer occurrence in control counties that were individually matched to the study counties. The mortality and incidence data pertaining to each facility were analyzed in specific time-periods, both before and after the facility became operational.

D. Methodologic Studies. Methods for increasing the usefulness of information from existing datasets and for resolving difficult analytic problems that arise during the course of other studies comprise this project area. In order to maximize the capability to locate persons currently who were exposed to radiation many years in the past, tracing methodologies are continually being developed and modified. Record-linkage collaborations have continued to utilize the resources of cancer registries around the world. The usefulness of personal computers in epidemiologic research has been evaluated.

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For certain well-studied cancer sites, attempts are made to strengthen inferences and to resolve apparent inconsistencies among different studies. This is accomplished by reanalyzing the basic data in parallel, in collaboration with the original investigators. This is being done for thyroid cancer and breast cancer incidence data from several exposed populations. Cohorts of underground miners exposed to radon are soon to be analyzed; several population-based case-control studies of lung cancer and indoor radon are currently being analyzed in parallel. The primary focus is on comparability of relative and absolute measures of radiation-related risk in populations with different baseline risk levels, and on integrated risk over the entire period of observation. A new statistical method was developed to enhance estimates of interaction between radiation and other risk factors in nested case-control studies of cancer, in which known dose-response relationships can be exploited by matching cases and controls on radiation dose. General relative risk techniques for analyzing dose-response models in matched case-control studies were further evaluated in studies of women given radiotherapy for uterine cancer.

E. Consultant Activities and Services on Expert Committees. Staff members are often called upon to serve as consultants or committee members for the National Council on Radiation Protection and Measurements, the Department of Energy, the Oak Ridge Associated Universities, the Environmental Protection Agency, the DHHS Subcommittee to Coordinate Federal Radiation Activities, the National Aeronautics and Space Administration, the Commission of the European Communities, the International Commission on Radiation Protection, the International Agency for Research on Cancer, the Radiation Effects Research Foundation, the World Health Organization, and chartered committees of the NCI. Such service can enhance the Branch research program by highlighting critical areas of uncertainty for risk estimation that may be the subjects of new epidemiological investigations.

F. Review Papers. Several review papers were written concerning health effects following exposure to ionizing radiation, including a comprehensive review of cancer following radiation exposure, risks following exposure to high-LET radiations, reviews of radiogenic bone and thyroid cancers, the relationship between nuclear energy and cancer incidence, the possible influence of genetic susceptibilities to radiogenic cancer, epidemiologic studies of cancer risks from low doses of ionizing radiation, the importance of latent period, risk projection and time-response models, problems of transporting risk estimates between populations with different baseline cancer rates, and the relative importance of different organ sites for radiation protection.

G. Workshops. A Collaborative Workshop on the Comprehensive Analysis of Thorotrast in a Whole Body, jointly sponsored by the National Cancer Institute and the United States Transuranium Registry, took place in July 1990. Various aspects of the donor's clinical course and autopsy findings were correlated with organ dosimetry of deposited radioactivity. The peer-reviewed proceedings are planned to be published in a forthcoming issue of Health Physics. Several workshops were held to discuss the progress of ongoing studies. The workshop on thyroid cancer following diagnostic x-rays included

investigators from Sweden and Oregon. The Workshop on second cancers following radiotherapy for uterine corpus cancer included investigators from Finland, Denmark, Canada, and Sweden.

Major Findings:

A. Medical Exposures.

1. A third follow-up of 13,385 tuberculosis patients treated between 1930-1954 in Massachusetts was completed and data were analyzed using Poisson regression methods. Approximately half of these patients received multiple chest fluoroscopies during pneumothorax treatment. Results indicated that repeated relatively low radiation doses pose a long-term risk of breast cancer, but not lung cancer or leukemia. Further evidence for the linearity of the dose-response for radiogenic breast cancer was strengthened as was the decreasing risk associated with increased age at exposure. A small, but dose-related, excess of basal cell carcinomas was identified following multiple x-ray fluoroscopies of the chest.
2. Radiation exposures to the scalp during childhood for ringworm were associated with a fourfold increase in skin cancer, primarily basal cell cancer, and a threefold increase in benign skin tumors. Risk was greatest following exposure in early childhood. This finding suggests the role that subsequent exposure to ultraviolet radiation likely plays in the expression of potential radiation-induced skin malignancy.
3. Cells with stable aberrations were detected with greater frequency in irradiated subjects from three populations exposed to partial body exposures compared to nonirradiated subjects. Findings from chromosome analyses of infants irradiated for suspected enlarged thymus glands, children irradiated for enlarged tonsils, and women exposed to multiple chest fluoroscopies all showed that stable aberrations appear to be informative as biological markers of exposure up to 30 years later.
4. Over 83,000 twins in Sweden were studied to evaluate further the association between x-ray exposure *in utero* and childhood cancer. In a nested case-control study, 95 cases of childhood cancer were matched to 190 cancer-free twins. Evidence of prenatal x-ray was found for 41% of the cases and 36% of the controls. More than half were abdominal x-rays, for which the relative risk was 1.4 for all childhood cancers, 1.7 for leukemia and 1.5 for central nervous system tumors. These risks are consistent with other studies and suggest that the developing fetus may be more sensitive to x-ray exposure than children irradiated postnatally. However, the risks were not statistically significant.

Record-linkage studies comparing childhood cancer incidence among twins with that of the general population (98% singletons) were conducted in Sweden and Connecticut. Because twins were more frequently exposed to diagnostic x-rays *in utero*, it had been thought that they might experience a higher cancer incidence. To the contrary, cancer occurred slightly (but not significantly) less often than expected based on

general population rates among the Swedish twins, and substantially less often than expected among the Connecticut twins. In both investigations, the deficit was apparent primarily among male twins. The reasons for these observations are unclear, but, together with other studies in the literature, they indicate that the baseline risk of childhood cancer is lower among twins than among single-born children. Nonetheless, it remains somewhat peculiar that twins who were frequently exposed prenatally to diagnostic x-rays would be at a lower overall risk of leukemia than single-born children who are less frequently irradiated *in utero*.

5. A SEER-based study of second cancers in women treated for non-Hodgkin's lymphoma (NHL) revealed increased risks for cancers of the stomach, bone, bladder, kidney, and lung, malignant melanoma, Hodgkin's disease, and acute non-lymphocytic leukemia (ANLL). Chemotherapy appeared related to subsequent ANLL and bladder cancer. Radiotherapy was associated with ANLL, and possibly cancers of lung, bladder, and bone. Malignant melanoma was not clearly related to initial NHL treatment. Comparisons with population rates indicated that NHL patients are at a significantly elevated risk (two- to fourfold) of subsequently developing Hodgkin's disease, but the risk did not appear to be related to treatment. Diagnoses of both NHL and Hodgkin's disease were confirmed in 9 of the patients.
6. In a case-control study within two prepaid health plans, there was no evidence that diagnostic x-rays increased the risk of developing chronic lymphocytic leukemia (CLL), a tumor that has never been linked with exposure to ionizing radiation. For cases with leukemia other than CLL, risk decreased to a normal level when exposures near the time of diagnosis were ignored, suggesting that many of the x-rays were given for conditions related to the early stages of leukemia. The non-Hodgkin's lymphoma cases were x-rayed significantly more often than controls, but no relationship was seen when recent exposures were excluded. This pattern suggests that the x-rays were administered for conditions arising during the early phases of lymphoma development. Overall, patients with multiple myeloma did not receive significantly more x-ray exposure than controls. However, the most heavily exposed were at significantly elevated risk regardless of the exposure-lag interval and there was evidence for a dose-response relationship.
7. Cancer mortality among 4,483 women irradiated for benign gynecologic disorders in Massachusetts or Rhode Island was 30% greater than expected based on U.S. mortality rates, and the excess occurred mainly among organs close to the radiation source. Statistically significant associations between mortality and dose were observed for leukemia and cancer of the colon. Less stable positive associations were seen for bladder cancer, and for cancer of nonuterine genital organs (mostly ovary) at ovarian doses greater than 1 Gy (100 rad). Mortality due to cancer of the uterus or cancer of the pancreas, though clearly elevated, was not associated with dose for either organ. It is likely that some of the gynecologic disorders for which these women were irradiated are

prognostic of increased risk for uterine cancer, and it is difficult to dissociate possible radiation effects from confounding effects associated with the presenting gynecologic conditions. Summary estimates of the excess relative risk attributable to radiation, expressed per Gy were 1.9 for leukemia, 0.5 for colon cancer, 0.2 for bladder cancer, 0.1 for nonuterine genital cancers, 0.0 for cancer of the rectum, and 0.0 for cancer of the uterus. For organs receiving > 1 Gy, cancer mortality remained elevated for more than 30 years, which supports the notion that radiation damage persists for many years after exposure. Contrary to findings for other populations treated by pelvic irradiation, a deficit of deaths due to breast cancer was not observed. Dose to the ovaries [(median, 2.3 Gy (230 rad))] may have been insufficient to protect against breast cancer. Chromosome analyses suggest that a larger fraction of aberrant stem cells survived per average unit dose in subjects irradiated for BGD compared to cervical cancer patients who received high, localized doses to the same region. These data are consistent with epidemiologic observations of a difference in the excess relative risk of leukemia in these two populations.

8. No excess of leukemia was found among 10,000 Swedish patients given therapeutic doses of ¹³¹I to treat hyperthyroidism, primarily Graves disease. Stomach cancer, however, appeared to increase with increasing radiation dose.
 9. The whole-body analyses of a woman given Thorotrast indicated that the distribution of Thorotrast in the bone-marrow was relatively uniform and perhaps accounted for the high leukemia risk seen; that the doses to breast tissue and to the eye were minimal; and that the doses to liver tissue and lymphocytic tissue were quite large and very nonuniform. Additional oncogene and tumor suppressor gene studies on selected tissues such as lung and liver are recommended. The measurement of radon-220 in exhaled air and the assay of various parameters of hormonal and immune function in long-term survivors might be valuable. The peer-reviewed proceedings of the Workshop will be published in a forthcoming issue of Health Physics.
 10. Fractionated exposure to radiotherapy for breast cancer averaging 7.2 Gy (720 rad) to the active bone marrow was associated with a significantly increased twofold risk of secondary acute nonlymphocytic leukemia. The highest risk was found for marrow exposures of more than 10 Gy (1000 rad).
- B. Atomic Bomb Survivors.
1. A case-control study of breast cancer has shown that the usual risk factors related to reproductive history, i.e., nulliparity, late age at first delivery, and number of children, are associated with risk in this population. These factors are highly correlated, but there is some evidence of independent effect. Number of children and total months of lactation were statistically significant risk factors even after adjustment for nulliparity and age at first delivery, but were highly

correlated with each other. Neither age at menopause nor age at menarche were significantly related to risk.

2. Reproductive history also affected the excess risk of breast cancer associated with radiation exposure, in that women at lower or higher risk than average on the basis of reproductive history were at proportionally lower or higher risk of radiation-induced breast cancer for a given exposure level. Women exposed to radiation before their first delivery were at greater risk of radiation-induced breast cancer than women of the same age, and with the same dose, who were already parous at the time of exposure, whereas no such association was observed among women who were not exposed to the bombings.
3. Soluble iron levels from nutrient assays of stored serum obtained in 1970-1972 were significantly lower among persons who later developed stomach cancer.
4. Hormonal assays of serum obtained from women who were post-menopausal suggest that levels of total and non-protein-bound estrogen may have been higher among women who later developed breast cancer.
5. Different lung cancer subtypes predominated among A-bomb survivors and Colorado Plateau uranium miners, but these differences could be explained in terms of smoking history and the likelihood of radiation etiology. Small cell carcinomas predominated at high doses in both populations, and in both, adenocarcinomas were less frequent. Squamous cell carcinoma, on the other hand, was relatively more frequent among heavy smokers, regardless of radiation dose.
6. Eight hundred twenty-six female breast cancer cases were observed in the study cohort for the period 1950-85. This represents an increase of about 262 cases since the previous series, through 1980; almost all of the increase occurred among women who were under age 20 at exposure. Evidence for dose-related excess cancer risk among women exposed before age 10, in particular, has been greatly strengthened.
7. Prevalences of both proliferative and non-proliferative benign breast disease were significantly associated with radiation dose in a study of breast tissue obtained at autopsy from women without clinical breast cancer.

C. Occupational and Environmental Exposures.

1. A manuscript describing the methodology and results of a health survey of over 143,000 radiological technologists was submitted to Cancer. The population was identified from the 1982 computerized files of the American Registry of Radiologic Technologists, established in 1926. Over 90,000 technologists responded to a lengthy optical scan mail questionnaire and an additional 14,000 completed an abbreviated telephone interview. Nearly 7,000 technologists were reported deceased. Radiation exposure information was obtained from employer records, and linkage with

the nation's largest commercial dosimetry company yielded exposure data on about 85,000 subjects. Nearly 4% of the respondents reported having a cancer, mainly of the skin (1,517), breast (665) and cervix (726). Preliminary results suggest increased risks for mortality from breast cancer but not leukemia or lung cancer. The incidence of thyroid cancer also appears to be elevated in this group.

2. Cancer incidence among 27,011 diagnostic x-ray workers in China was 21% greater than expected based on the experience of 25,782 physicians who did not routinely use x-rays. This is less than the 50% excess reported previously, based on five fewer years of follow-up. The difference reflects, in part, the reduced risk among workers first employed after 1965, when hospital exposures probably were lower than in earlier years. The risk for leukemia was highest 10 to 15 years after employment began. Leukemia results are readily interpretable in terms of a declining secular trend in radiation exposure among x-ray workers and a wavelike pattern of excess leukemia risk following radiation exposure. Large excesses were recorded for esophageal and liver cancer, but there was little evidence that radiation was responsible. Excesses also were observed for cancer of the skin, which has been reported increased among radiologists in other studies, and cancers of the breast and thyroid. Excesses were not seen for cancers of the lung or pancreas, or multiple myeloma, cancers which have been reported increased in previous studies of radiologists in the United States and United Kingdom.
3. No association between lung cancer and residential radon was found in a study of over 300 women who developed lung cancer in China despite relatively high exposures (20% over 4 pCi/l). The data suggested that the risk projections from studies of underground miners and/or exposure assessment models may not be appropriate for estimating risks for women in this study. An increased risk of lung cancer with residential radon was suggested among women in Sweden, but the risk decreased appreciably when adjusted for occupancy.
4. The study of the occurrence of cancer in the vicinity of nuclear facilities in the United States was published. In the period 1950-1984, there were more than 37,000 deaths attributed to leukemia and more than 835,000 deaths from other cancers in the study counties, and nearly two million cancer deaths in the control counties. However, despite these large numbers, the analysis could find no evidence in any age group or in the whole population, that mortality from leukemia, or any other form of cancer, was increased as a result of proximity to any particular facility, or facilities generally, or facilities of any particular type, such as reprocessing plants or weapons plants or early electric generating stations. In fact, the relative risk of death from cancer tended to be lower after the facilities came into service than before. The conclusion was that, if any of the facilities were the cause of excess deaths in neighboring populations, the excess deaths were too few to be detectable.

5. Neutron exposures to 191 well loggers at four oil fields in China were measured over a three month period using CR-39 polycarbonate dosimeters. Workers engaged in well logging on an average 17 days during this interval. Cumulative neutron exposures were below the minimum detectable level of 0.02 mGy (2 mrad) for 184 workers. Readings for the other seven workers averaged 0.10 mGy (10 mrad). Doses were slightly lower than literature values for well loggers in North America, possibly because of differences in drilling activity. Because doses are so low, an epidemiologic study of cancer among Chinese well loggers is unlikely to be informative about the carcinogenicity of neutrons relative to sparsely ionizing radiation.
- D. Methodologic Studies.
1. A case-control interview study of breast cancer among A-bomb survivors involved the development of a new method for estimating interaction between radiation dose and other risk factors because matching was done with respect to dose. The method is more powerful than conventional analyses in which matching does not depend on dose.
 2. A comprehensive package of programs for epidemiologic analysis is nearing completion for use on microcomputers. Preliminary computer disks of "Epitome: Epidemiologic Analysis with a Personal Computer" have been distributed.
 3. Analyses of breast cancer incidence following radiation exposure were carried out in parallel, using new data from the Japanese A-bomb survivors, the original and extended Massachusetts fluoroscopy series, the Canadian fluoroscopy series, and the New York acute postpartum mastitis study. These analyses suggested significant differences in exposure-age-specific relative risks per unit dose between the North American and Japanese data, but that absolute risks were remarkably similar among the cohorts. This finding has important implications for the difficult, but crucial problem of transporting risk estimates between populations with different underlying cancer rates.
 4. A joint analysis of eight cohorts showing evidence of radiation-induced thyroid cancer is underway. Additional organ dose estimates have been made and the basic data are being reanalyzed in parallel using identical categories and definitions where possible. Using this common statistical approach, the large number of tumors and the wide variation in host and radiation factors is allowing us to address issues of dose- and time-response with precision. Preliminary results suggest that the risk of radiation-associated tumors may decline after 35 years.
 5. Generalized relative risk equations were applied to the study of leukemia following cervical cancer irradiation. A good fit was found for a model linear in dose which included a negative exponential term. These analyses suggest the importance that cellular killing or inactivation may play in defining dose-response relationships, at least for very high therapeutic doses.

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CONTRACTS IN SUPPORT OF THIS PROJECT

ENERGY, DEPARTMENT OF (Y01-CP-80505)Title: Studies on Radiation-Induced Chromosome Damage in HumansCurrent Annual Level: \$65,133Person Years: 2.8

Objectives: (1) To assess the utility of stable chromosome aberrations as a biodosimeter for partial-body exposures; (2) to contrast the dose-response relationship of the frequency of stable aberrations per unit dose following acute, chronic, whole-body and partial-body exposures; (3) to compare dose-response relationships with cancer risks in the same population; and (4) to compare *in vivo* with *in vitro* data on the relative biological effectiveness (RBE) of 14 MeV neutrons in inducing chromosome aberrations.

Methods Employed: Chromosomal aberrations are being identified and scored using classical cytogenetic non-banded methods. Blood samples have been collected from 900 subjects selected from among six populations exposed to partial-body diagnostic and therapeutic radiation during the period 1930-1970, which are currently under study by the Branch for cancer risk in relation to individual dosimetry. These populations include cervical cancer patients given radiotherapy, tuberculosis patients given multiple chest fluoroscopies, persons irradiated for lymphoid hyperplasia during childhood, persons irradiated for enlarged thymus glands during infancy, women irradiated for benign gynecologic disorders, and cancer patients treated with neutrons. Blood samples from control persons from each of these populations were obtained when possible. *In vitro* dose-response curves were generated for neutrons. All blood specimens are cultured, karyotyped and scored at the DOE-supported radiation cytogenetic laboratory at the Oak Ridge Associated Universities.

Major Contributions: To date, over 120,000 metaphases (200 cells per subject) have been scored for 159 tonsil patients, 287 cervical cancer patients, 150 tuberculosis patients, 202 patients treated as children for enlarged thymus glands, 64 women irradiated for benign gynecologic disorders (BGD), and 15 cancer patients treated with neutrons. A paper describing the results from 3 of the populations was published in Radiation Research. A small, but statistically significant difference in the frequency of stable chromosome aberrations was found in exposed persons as compared with nonexposed persons treated during childhood for enlarged tonsils or enlarged thymus gland and exposed tuberculosis patients compared with those who received other therapies. A paper on the findings in the BGD patients was presented at an international symposium on biosdosimetry and was published in the proceedings of that meeting. Irradiation for BGD appeared to induce a larger fraction of chromosomally aberrant stem cells surviving per unit dose compared to cervical cancer patients who received high, localized exposures to the same region of the body.

SURVEY RESEARCH ASSOCIATES (N01-CP-71096-02)

TITLE: Case-control Study of Residential Exposure to Radon

Current Annual Level: \$279,000

Person Years: 3.0

Objectives: To evaluate the relationship between residential radon exposure and lung cancer in nonsmoking women.

Methods Employed: About 600 nonsmoking female lung cancer cases are to be enrolled between January 1987 and May 1992 as reported to the Missouri Cancer Registry. Control subjects for cases under the age of 65 are being selected from the state drivers license registry and for those 65 and older from files of the Health Care Financing Administration. Alpha-track radon detectors are being placed in the current and prior residences of study subjects for a full year to eliminate seasonal variation in the measurements.

Major Contributions: A rapid ascertainment system is in operation, which allows data to be collected soon after diagnosis while the majority of the cases are still alive. Controls are being enrolled concurrently with the cases. To date, interviews have been completed with 100% of the cases (or their next-of-kin) and 86% of the controls. The non-cooperating controls are being replaced. Radon detectors have been recovered from 1,837 (93%) of the 1,975 time-eligible residences.

A pilot study was successfully performed (funded separately through an Interagency Agreement with the Department of Energy) to assess the feasibility and utility of placing strips of plastic film (CR 39) on glass items in the home from which to estimate cumulative radon exposure. Glass items that have been in the possession of the study subject for 20 or more years were measured for radon exposure. Two of three scheduled pathology reviews were completed.

TEXAS, UNIVERSITY OF, M.D. ANDERSON HOSPITAL (N01-CP-95614)

Title: Radiation Dosimetry for Epidemiologic Studies

Current Annual Level: \$207,325

Person Years: 3.4

Objectives: To evaluate radiation exposure circumstances and to determine whether data are adequate to calculate organ doses. If so, to estimate radiation doses received by body organs or tissues.

Methods Employed: The contractor provides the support necessary to make measurements on patients, anthropomorphic phantoms, or water phantoms in order to reconstruct radiation doses to specific organs following exposures. The contractor: (1) determines the manner in which physical dosimetry can be best

applied to the epidemiologic studies of interest; (2) coordinates dosimetry data collected or prepared by other medical physicists who are participating in our studies; (3) provides estimates of neutron dose distributions from betatrons and other high energy linear accelerators, as well as from primary neutron sources; (4) compares measured doses with calculated organ doses to validate consistency and accuracy of simulation models. Measurements are made to allow a separation of organ doses into the contribution from (a) head-leakage and collimator scatter, and (b) scatter within the patient from the useful beam.

Major Contributions: The contractor has developed and refined a measurement program to obtain organ-specific doses for (1) studies of cancer following childhood cancer treatment with radiation; (2) leukemia and lymphoma following diagnostic x-ray procedures; (3) contralateral breast cancer following radiotherapy for an initial breast tumor; (4) cancer following radiotherapy for benign and malignant gynecologic disorders; (5) cancer following neutron therapy; (6) patients undergoing multiple x-rays for scoliosis; (7) leukemia following radiotherapy for breast cancer; (8) thyroid cancer following irradiation for enlarged tonsils and other benign head and neck conditions; (9) cancer following radiotherapy for tinea capitis; (10) cancer following radiotherapy for retinoblastoma; (11) cancer following irradiation for peptic ulcer; (12) cancer in x-ray technologists; (13) cancer in women irradiated for infertility; (14) leukemia following radiotherapy for endometrial cancer; and (15) thyroid cancer following thymic irradiation.

WESTAT, INC. (N01-CP-85604)

Title: Support Services for Radiation and Related Studies

Current Annual Level: \$1,800,000

Person Years: 12.5

Objectives: To provide all aspects of field support (technical, managerial, and clerical) for epidemiologic studies. The contractor functions in a supportive role carrying out specific tasks assigned by the Branch and does not engage in independent research.

Methods Employed: All types of support services are being obtained, including: (1) preparing data collection forms; (2) preparing manuals for abstracting, coding, interviewing, and tracing; (3) tracing individuals to determine vital status; (4) obtaining consent of study subject to be interviewed; (5) interviewing or sending mail questionnaires; (6) obtaining death certificates; (7) abstracting, keying, editing, updating, and coding of data; (8) occasionally transporting biological specimens; (9) assessing exposure information; and (10) creating and manipulating data files.

Major Contributions: The contractor has provided support services for the following studies: (1) patients treated with radioactive iodine for Graves disease (hyperthyroidism); (2) the follow-up study of cervical cancer patients treated in U.S. clinics; (3) questionnaire preparation, tracing, and data file preparation for the x-ray technologist study; (4) leukemia case-control study

among breast cancer patients reported to selected Surveillance, Epidemiologic, and End Results cancer registries; (5) ongoing follow-up and tracing for the TB-fluoroscopy breast cancer studies in Massachusetts and Connecticut; (6) study of cancer following radiotherapy for infertility in New York; (7) cohort study of children irradiated for enlarged tonsils in Chicago; (8) tracing support, glycophorin-A mutation assays, and chromosome studies on peripheral bloods of women irradiated for benign gynecological disease; (9) feasibility study of workers in China exposed to neutrons; (10) feasibility study of nuclear power workers; (11) study of second cancers following treatment for retinoblastoma; (12) hormonal studies of cervical cancer patients; (13) second cancers following treatment for non-Hodgkin's lymphoma; (14) study of leukemia following radiotherapy for uterine corpus cancer; (15) feasibility study of patients treated with neutrons; (16) tracing support for study of persons in Chicago irradiated for peptic ulcer; (17) mortality survey of persons living in counties near nuclear facilities; and (18) management of all tracing activities for the Epidemiology and Biostatistics Program.

WESTAT, INC (N01-CP-85651)

Title: Breast and Other Cancers Following X-Rays for Scoliosis

Current Annual Level: \$192,123

Person-Years: 1.8

Objectives: Girls with scoliosis or other curvature of the spine receive multiple diagnostic x-rays during childhood and adolescence to monitor the progression of the spinal curvature and the effects of treatment. These are ages when the breasts may be especially susceptible to radiation-induced carcinogenesis. The risks of breast and other cancers among patients with scoliosis have not been previously studied. The risk of breast cancer associated with various factors, such as low-dose fractionated exposures and age at exposure will be evaluated as will the possible interactions with the biological processes of menarche and breast development. Information on important breast cancer risk factors, such as age at menarche, family history, and age at birth of first child, will be obtained so that all risks may be appropriately evaluated. All cancers will be studied, but emphasis will be given to breast, leukemia, lung, and thyroid cancers.

Methods Employed: Twenty-three orthopedic medical centers with relatively large populations were identified for possible inclusion in this study. Site visits were made to evaluate the number of female subjects diagnosed before 1966 and the availability of their medical records and x-rays for review. Patients from ten hospitals were enrolled. Information from the patient records was abstracted on demographic data, scoliosis diagnosis and treatment, medical history of other conditions, number and kind of x-ray examinations, and location information. Patients are being located using all available tracing resources, including motor vehicle departments, credit bureaus, telephone directories, vital statistics records, the Social Security Administration mortality files, Health Care Financing Administration records, state death tapes, National Death Index searches, contacts with relatives, marriage certificates, and other

sources, as appropriate. The possible role that a germ line defect in the p53 tumor suppressor gene might play in radiogenic breast cancer is to be evaluated.

Major Contributions: Patients from ten institutions have been enrolled. The centers include seven Shrine Hospitals (Springfield, Philadelphia, Chicago, Portland, San Francisco, St. Louis, and Greenville), Boston Children's Hospital, DuPont Institute, and Elizabethtown Hospital and Rehabilitation Center. Medical records have been abstracted and x-rays reviewed. The expanded study population is comprised of 4,608 eligible women treated for scoliosis before 1966. The total study population, including 1,030 women from the pilot study in Minneapolis-St. Paul is 5,638. Social security numbers were found for 88% of subjects to date. A total of 214 subjects have been reported deceased.

INFORMATION MANAGEMENT SERVICES, INC. (N01-CP-05609)

Title: Biomedical Computing Support for Radiation Epidemiology Branch

Current Annual Level: \$299,329

Person-Years: 5.0

Objectives: Contractor staff provide biomedical computing support for the epidemiologic and methodologic studies conducted by the Radiation Epidemiology Branch.

Methods Employed: Contractor tasks include: capturing data to be incorporated into new or existing data bases (i.e., data abstraction, coding, keying, and/or receipt of data from other contractors on magnetic media); performing quality control (using such techniques as sampling, control totals, hand verification of data, creation of specialized test files, use of structured programming techniques, use of self-proving code, and comparison of new with previous results); developing and programming comprehensive field edit and cross field edit algorithms for application against new and existing data bases; editing data, reconciling errors, and updating files with correct values, as appropriate; designing and creating efficient data analysis files for use by statistical reporting and analysis programs; programming statistical reports and data analysis as requested by Radiation Epidemiology Branch investigators; developing and maintaining indexed documentation of data files and computer programs; conducting research and development in personal computer software for supporting epidemiologic and methodologic studies; and providing technical support for PC hardware.

Major Contributions: Over 30 projects have been supported during the period covered by this report. On average, biomedical computing support is provided for 17 projects per month. They include large cohort follow-up studies, case-control studies, drug and multiple primary studies, population and rate studies, measurements and risk assessment, and methods and software development. Significant progress has been made on numerous studies. Ad hoc meetings are held with REB investigators, as needed, to discuss specific tasks required. Routine telephone contact is maintained. Contractor personnel meet formally with the Project Officer and other REB investigators monthly to determine the

status of on-going efforts, discuss problems, and make decisions about pending tasks. Priorities are established and reevaluated each month.

WESTAT, INC. (N01-CP-95608)

Title: Support Services for Childhood Leukemia and Residential Electromagnetic Fields (EMF)

Current Annual Level: \$1,012,896

Person-Years: 13

Objectives: The primary objective is to examine the relationship of childhood (including pregnancy-related) residential exposure to extremely low frequency electromagnetic radiation and radon with the development of acute lymphocytic leukemia (ALL) in children, focusing on possible associations of EMF with specific ALL biologically-defined subgroups. This is one component of the large-scale study of ALL being conducted by the Children's Cancer Study Group (CCSG).

Methods Employed: Mothers of about 600 ALL cases in the NCI-CCSG EMF study component, which include cases diagnosed and treated in CCSG-affiliated hospitals in one of six states (Pennsylvania, Ohio, Indiana, Illinois, Michigan and Minnesota), and mothers of 600 matched controls will be interviewed at home. Exposure measurements will be obtained in all residences where the subject lived for a year or more since conception. Measurements will include spot electric and magnetic field measurements in three key rooms, measurements of the geomagnetic field, 24-hour magnetic field measurements in the child's bedroom, and standardized wire coding of the residentially proximate power line configurations. Radon detectors will be placed in all residences as well. Information about potential confounders will be assessed. The contractor is providing support services to carry out all data collection components for the study, with technical aspects of measurement procedures developed and operationalized by the subcontractor under the leadership of Dr. William Kaune.

Major Contributions: Results from the pilot study indicated that spot measurements are highly correlated with measurements from personal dosimeters worn by children, and that out-of-home exposures explain little of the variability in a child's exposure. A measurement algorithm was developed based on these findings. A 24-hr measurement in the subject's bedroom will be made as well as spot measurements under low and regular power conditions in three rooms in the subject's home. No measurements are planned in schools or day care centers. Results of the pilot study and measurement protocol were reviewed and approved by the Advisory Group to the study at their second meeting. The group also recommended taking a measurement in the pregnancy bedroom if possible. The Environmental Protection Agency will fund the radon component of the study. Radon detectors will be placed in all lifetime residences to the extent possible. Development of the mother's questionnaire was completed and clinical exemption from OMB clearance was approved by NIH.

TECH/OPS LANDAUER (N01-CP-95651)

Title: Dosimetry Support for Studies of Radiation Workers

Current Annual Level: \$36,218

Person-Years: 0.3

Objectives: The objectives of this project are: (1) to obtain cumulative dose estimates for studies of radiation workers, in particular for our ongoing follow-up investigation of over 145,000 x-ray technologists registered by the American Registry of Radiologic Technologists; and (2) to utilize the existing system of records to establish a dosimetry registry of approximately 250,000 radiation workers who were employed in 1978 and later, and for whom reasonably accurate estimates of cumulative exposures are available.

Methods Employed: Tech/Ops Landauer has been providing monthly radiation dosimetry determinations for more than half the radiation workers in the United States since the early 1950s. The unique characteristic of the Tech/Ops Landauer records is that estimates of cumulative radiation doses can be assigned to every individual in their files. The Contractor will provide the support necessary for developing all materials and procedures to: provide ongoing support for the study of 145,000 x-ray technologists by supplying estimates of cumulative radiation doses; establish a dosimetry registry of radiation workers who were enrolled for dosimetry services in 1978 through the present; provide appropriate listings of these radiation workers who have terminated their dosimetry services, including dates of termination and cumulative radiation doses; provide necessary computer files to link terminated radiation workers to the National Death Index and other appropriate mortality records and validate any matches provided; and provide yearly and cumulative dose data, and demographic and occupational data as necessary to evaluate mortality in relation to occupational histories.

Major Contributions: A registry of 252,000 radiation workers was developed and linked with the Tech/Ops Landauer dosimetry records for 1978-1984. The same individuals have been linked with records for five additional years (1985-1989) to obtain a cumulative radiation exposure for the entire period. Nearly 47,000 (18.6%) were active users of the Landauer dosimetry service during all 12 years. About 60% were active during five or more years. A separate population of 144,533 x-ray technologists was linked with the dosimetry records for the years 1985-1989 (this population had also been linked previously with the 1978-1984 records). Dosimetry records for one or more years during the entire time period were found for 84,491 technologists (58.5%). Seventy-two percent of these had dosimetry data retrieved for five or more years, and 15% had data retrieved for all 12 years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01CP05368-08 REB

PERIOD COVERED

October 1, 1990 to September 30, 1991

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Studies of Drug-Induced Cancer and Multiple Primary Cancers

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.D. Boice, Jr.	Chief	REB	NCI
Others:	R.E. Curtis	Statistician	REB	NCI
	R.A. Kleinerman	Epidemiologist	REB	NCI
	M.A. Tucker	Chief, Family Studies Section	EEB	NCI
	L.B. Travis	Pathologist	REB	NCI

COOPERATING UNITS (if any)

Danish Cancer Registry (O. Jensen); M.D. Anderson Hospital (M. Stovall)

LAB/BRANCH

Radiation Epidemiology Branch

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

3.5

PROFESSIONAL:

3.0

OTHER:

0.5

CHECK APPROPRIATE BOXES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to evaluate the carcinogenic potential of medical treatment with drugs. Since many cancer patients are exposed to both radiation and cytotoxic agents, these studies are a logical extension to the Branch's study of radiation-induced second cancers. In addition, other non-therapeutic drugs are studied when of special interest. The Branch also conducts studies of multiple primary cancers in order to generate hypotheses about host and environmental determinants of specific cancers. Populations under study include cancer patients reported to population-based cancer registries (especially the SEER Program), persons treated at major institutions, and those treated in randomized clinical trials. Additional details on collaborative projects can be found in Project No. Z01CP04412-15 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CP04410-15 EEB, "Studies of Persons at High Risk of Cancer."

Breast cancer patients treated with alkylating agents had an increased risk of leukemia that depended on type of drug administered. Risk was highest for patients receiving the highest doses and for those treated with both radiotherapy and cytotoxic drugs. A cancer registry study found that chemotherapy for non-Hodgkin's lymphoma was related to subsequent leukemia and bladder cancer. Anti-convulsive drugs used to treat epilepsy were not found to increase the overall risk of cancer, although slight increases in lung cancer and non-Hodgkin's lymphoma were noted. Children of epileptic mothers exposed to anti-convulsive drugs were not at increased risk of cancer. Children treated for retinoblastoma were found to be at very high risk of dying from a second cancer before reaching the age of 40 years, especially those with bilateral disease. Radiotherapy further increased the risk of second cancers, especially osteosarcomas. Radiotherapy for childhood cancer was linked to a high risk of thyroid cancer.

PROJECT DESCRIPTIONNames, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

John D. Boice, Jr.	Chief	REB	NCI
Rochelle E. Curtis	Statistician	REB	NCI
Lois B. Travis	Pathologist	REB	NCI
Ruth A. Kleinerman	Epidemiologist	REB	NCI
Michele Morin	Epidemiologist	REB	NCI
Martha Linet	Medical Staff Fellow	BB,DCE	NCI
Margaret A. Tucker	Chief, Family Studies Section	EEB	NCI
Robert N. Hoover	Chief	EEB	NCI
Joseph F. Fraumeni, Jr.	Associate Director	EBP	NCI
Dana R. Friedman	Epidemiologist	REB	NCI
Benjamin F. Hankey	Statistician	DCPC	NCI
Frederick P. Li	Chief, Clinical Studies Sec.	CEB	NCI

Objectives:

(1) To clarify the magnitude and determinants of risk of second cancers after chemotherapy. (2) To study the long-term effects of selected drugs in humans and to characterize risk in terms of dose and latent period as well as the influence of age, sex and race. (3) To evaluate the causes of multiple primary cancers.

Methods Employed:

1. The Radiation Epidemiology Branch collaborates with NCI's Environmental Epidemiology Branch and the Division of Cancer Treatment, to conduct studies on the late carcinogenic effects of cytotoxic therapies for cancer patients (see also Project No. Z01CE04412-15 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CE04410-15 EEB, "Studies of Persons at High Risk of Cancer"). Several NCI-supported randomized clinical trials have been identified that have evaluated drugs of special interest. Contacts have been made with clinical trial group chairmen and statisticians to obtain the needed data from computerized files. Several groups are collaborating with NCI on this project: the Gynecologic Oncology Group, the Veterans Administration Surgical Oncology Group, the Gastrointestinal Tumor Studies Group, and the Brain Tumor Study group. In addition, studies have been initiated or are in the planning stage at several major cancer centers, such as M.D. Anderson Hospital in Texas and Princess Margaret Hospital in Canada. To date, agents under evaluation include BCNU, melphalan, methyl-CCNU, cisplatin, cyclophosphamide, thiotepe, chlorambucil, 5-fluorouracil, and adriamycin, among others.
2. A case-control study of 220 children with second malignant neoplasms and 400 controls has been completed. These children were treated with a

wide range of chemotherapeutic agents. Analyses for cancers of the thyroid, brain and connective tissue are ongoing.

3. A study of leukemia following treatment for breast cancer involving four U.S. registries has been completed. Record linkage identified 90 cases of secondary leukemia and preleukemia among breast cancer patients. A detailed case-control study compared the treatment history between cases and 264 matched breast cancer controls. Analysis of these data is ongoing.
4. Parallel case-control analyses have been conducted using data from Danish and U.S. cancer registries to investigate the etiology of endometrial cancer among women previously treated for breast cancer. Preliminary analysis of the 292 U.S. cases and their matched controls was completed.
5. Prescription drug use and risks of leukemia, lymphoma, and multiple myeloma are being examined in a medical record study of cases and controls in two pre-paid health plans. Adult patients with leukemia (n=299), non-Hodgkin's lymphoma (n=100), and multiple myeloma (n=175) were matched to controls (n=787) within the same health plan on the basis of sex, age, calendar year of health plan entry, and length of membership. Information was abstracted from outpatient and hospital inpatient records on the use of specified oral and parenteral prescription drugs. The possible interaction of drug use with history of prior medical conditions is also being evaluated.
6. Data are being analyzed from the Veterans Administration's clinical trials system to evaluate the risk of second cancer among patients with colorectal cancer or lung cancer who received nitrogen mustard, cytoxan, methotrexate, or CCNU.
7. Danish epileptic patients who received phenobarbital, dilantin, and other anti-convulsive drugs have been evaluated for cancer risks. Children exposed *in utero* to anti-convulsive drugs are being followed for late effects. Cancer registry records have been linked with hospital lists to ascertain cancers. Case-control studies are ongoing to document drug exposure for epileptics who developed liver cancer, lung cancer and non-Hodgkin's lymphoma. Thorotrast exposure is also being studied.
8. A record-linkage study of second cancers following treatment for cervical cancer was initiated to provide new information on the pattern of cancer risk over time, especially for long-term survivors. A cohort of approximately 50,000 patients will be assembled from population-based tumor registries to investigate the effects of radiotherapy 30 years and more after treatment.
9. An ongoing project is a survey of the SEER registry database to identify treatment-induced second primary cancers. Of particular interest is the

risk of second solid tumors following chemotherapy. The role of adjuvant tamoxifen therapy used to treat breast cancer is being evaluated in the subsequent development of endometrial cancer. Several other cancer sites commonly treated with chemotherapy are being investigated: Hodgkin's disease; non-Hodgkin's lymphoma; chronic lymphocytic leukemia; multiple myeloma; leukemia; and cancers of the ovary, lung, and testis.

10. A second follow-up of patients treated with BCNU (carmustine) for brain tumors is being initiated to provide additional information about the toxicity of nitrosourea compounds. Follow-up of survivors from the original study population will be extended and this experience will be supplemented by that of patients from several new clinical trials. The occurrence of leukemia and preleukemia following exposure to carmustine is of particular interest.
11. Data from the SEER cancer registries were analyzed to characterize the risk of second cancers in patients treated for non-Hodgkin's lymphoma, with an emphasis on subsequent solid tumors.
12. A cohort of over 100,000 patients with uterine corpus cancer is being evaluated to identify increased risk of second cancers. Data has been obtained from 13 cancer registries in the United States, Europe and Canada. Second cancer risk will be evaluated by type of treatment, age and year of uterine corpus cancer diagnosis, race, time after treatment, and type of endometrial cancer.
13. The risk of second primary cancers is being evaluated in over 9,000 patients with chronic lymphocytic leukemia reported to the NCI Surveillance, Epidemiology, and End Results (SEER) Program. Of particular interest is the risk of subsequent cancer associated with chemotherapy.
14. Over 3,000 women with breast cancer who participated in several early (1958 - 1968) randomized clinical trials conducted by the National Surgical Adjuvant Breast And Bowel Project (NSABP) have been followed for cause-specific mortality. These subjects were randomized to receive one of several treatments, including low-dose chemotherapy and placebo, following Halsted radical mastectomy. This cohort is anticipated to provide information with regard to the baseline risk of leukemia following breast cancer.
15. A multi-center study of second cancers following non-Hodgkin's lymphoma (NHL) is planned. Record-linkage techniques will be utilized to estimate the risk of second primary cancers in 2-year survivors of NHL. The dose-response relationship between the occurrence of second cancers and the administration of chemotherapy and/or radiotherapy will then be estimated. This study will utilize a variation of the case-cohort design: detailed treatment information will be abstracted only for those sites in which significantly elevated risks of cancer are noted, and for a random sample of all members of the eligible cohort.

16. The risk of secondary breast cancer following radiotherapy for breast cancer is being evaluated in Connecticut and Denmark. Radiation exposure histories are being reconstructed and possible dose-response relationships evaluated.

Major Findings:

1. Breast cancer patients treated with alkylating agents had an increased leukemia risk that differed by the type of agents administered. A significant dose-response relationship was established for several alkylating agents. Risk was especially high for patients treated with both radiotherapy and alkylating agents.
2. A review of second cancers reported to the SEER registries found that the risk of leukemia was increased following chemotherapy for small cell lung cancer, breast cancer, ovarian cancer, testis cancer, Hodgkin's disease, non-Hodgkin's lymphoma, and multiple myeloma.
3. Long-term survivors of non-Hodgkin's lymphoma were at especially high risk to develop a second primary cancer. Significant excesses were noted for leukemia, melanoma, Hodgkin's disease, and cancers of the bladder, kidney, and lung. Chemotherapy appeared related to subsequent acute nonlymphocytic leukemia and bladder cancer.
4. Children of epileptic mothers who received heavy and continuous exposure to anti-convulsive drugs, such as phenobarbital, were not found to be at increased risk for childhood cancer.
5. A study of patients with breast cancer found a small, nonsignificant association between use of menopausal estrogens and risk of endometrial carcinoma and a significant two- to threefold risk associated with use of estrogens in breast cancer treatment.
6. Patients with chronic lymphocytic leukemia had a significant increase in all subsequent cancers with elevations evident for malignant melanoma, Hodgkin's disease, non-Hodgkin's lymphoma, and cancers of the lung, eye, and brain.
7. Children treated with high-dose radiotherapy for cancer were found to be at increased risk for developing thyroid cancer.
8. Children treated for retinoblastoma were at very high risk of dying from a second cancer before reaching the age of 40 years, especially those with bilateral (or heritable) disease. Radiotherapy further increased the risk of second cancers, notably osteosarcomas.

Publications:

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Travis LB, Curtis RE, Boice JD Jr, Hankey BF, Fraumeni JF Jr: Second cancers following non-Hodgkin's lymphoma. Cancer 1991;67:2002-9.

Tucker MA, Morris Jones PH, Boice JD Jr, Robison LL, Stone BJ, Stovall M, Jenkin RDT, Lubin JH, Baum ES, Siegel SE, Meadows AT, Hoover RN, Fraumeni JF Jr. Therapeutic radiation at a young age is linked to secondary thyroid cancer. Cancer Res (In Press).

ANNUAL REPORT OF
THE EXTRAMURAL PROGRAMS BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1990 through September 30, 1991

The Extramural Programs Branch (EPB) plans, develops, directs and manages extramural research in biometry, epidemiology, genetic epidemiology, and related multidisciplinary activities. This includes the evaluation of program effectiveness; the provision of information about funding from the National Institutes of Health (NIH) and the National Cancer Institute (NCI); advising the NCI about funds needed for research administered by the Branch, and developing new initiatives as needed; managing the research resources necessary for a coordinated research program; and meeting with investigators to exchange scientific information and keep abreast of research trends.

The EPB is responsible for grants, cooperative agreements, and contracts focused on cancer epidemiology, genetic epidemiology, and biostatistics. Of these, the greatest reliance is on research grants. For several years, the Branch has actively encouraged multidisciplinary approaches to research in these areas. Currently, the Branch administers 207 grants, divided among several components directed by six scientists (Fig. 1).

Biometry: The extramural biometry program supports the development of statistical methods for the design, conduct and analysis of epidemiologic and biomedical studies in oncology. The overall goal is to apply these disciplines to foster delineation of mechanisms of cancer etiology. Some particular goals of theoretical biostatistical projects are to develop analytical techniques to improve clinical trials and risk assessment, to identify genetic-environmental contributions to diseases, and to extrapolate environmental exposure from species to species and from high to low dosages. The Branch will be sponsoring a workshop in July 1991, to discuss how recent developments in theoretical biostatistics and computing can best be incorporated into the resources for analysis (e.g., statistical packages) available to epidemiologists.

Epidemiology: Research interests in this program include the natural history of neoplasia in humans, geographic variation in incidence and prevalence of cancers, the definition of risk factors for cancer, development of information basic to cancer prevention, and the development of new methods which improve the precision and accuracy of epidemiologic studies.

During the previous year, in collaboration with the Organ Systems Program of the Division of Cancer Biology, Diagnosis, and Centers, the program participated in supporting an international workshop on the epidemiology and biology of multiple myeloma. The workshop proceedings were edited by EPB staff and are being published as a monograph.

As a result of a Branch workshop, a Request for Application (RFA) was issued to stimulate epidemiologic studies and provide additional insights into the causes of cancer among ethnic/minority groups by delineating similarities and differences in cancer risks. Over 50 grant applications resulting from this RFA are currently under review, and the Branch anticipates funding 5-8 new research projects in this area of high priority.

Cancer incidence and mortality rates in the aged have not shown much improvement over time for most cancer sites. The Branch expects to organize a workshop to focus attention on the distribution and pathogenesis of cancers associated with the aging process.

Genetic Epidemiology: The genetic epidemiology program supports projects on the interaction between somatic and genetic alterations and environmental exposures in the etiology of cancer. Research focuses on the analysis of genetic susceptibility for various tumors, and on the study of risk factors in familial clusters of cancer-related diseases. A conference on genetic epidemiology to address methodological developments and analytic needs is under development for the winter of 1991-92.

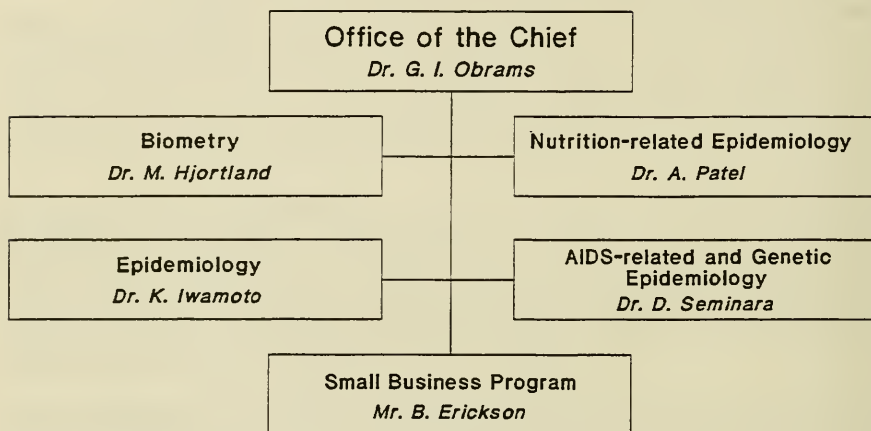
Biochemical/Molecular Epidemiology: The biochemical epidemiology program encourages the development and application of laboratory methods specifically for epidemiologic studies of cancer etiology. Efforts are focused on the identification and validation of biomarkers reflecting host susceptibility and/or exposure to carcinogenic agents. In conjunction with a conference on these topics being organized by the International Agency for Research on Cancer, the Branch is planning to hold a workshop in October 1991, to define epidemiologic research directions in this program area.

Viral Epidemiology: This program emphasizes the epidemiologic study of risk factors and mechanisms associated with human papillomaviruses (HPV) and hepatitis B virus (HBV). The objective of the program is to establish the incidence, natural history, and risk factors for malignancies and pre-malignant conditions associated with viral infections.

Retroviral and HIV-Related Epidemiology: The overall objective of this program is to establish the incidence, natural history, and risk factors for malignancies and premalignant conditions associated with retroviral infections, including the human immunodeficiency virus (HIV). Of particular interest are studies on the effect of viral strain variation, co-infections with multiple viruses, genetic factors, immune alteration, anti-viral treatments and environmental exposures on the development and progression of virus-associated neoplasia. In March 1991, the Branch held a meeting of grantees working in AIDS-related research, which resulted in the communication of data from work in progress and sharing of research resources and questionnaires. Abstracts from this meeting will be prepared in a bound format. Future plans emphasize the HIV-associated cancer risks in women and children and continuation of current efforts to define the pathogenesis of Kaposi's sarcoma, lymphomas and squamous cell tumors in HIV-infected individuals.

Small Business Innovation Research (SBIR) Program: The Branch is shifting its position slightly to encourage grant rather than contract submissions from small businesses under the SBIR program. Fostering small business participation in Federal research and development is an important commitment to a congressionally-mandated initiative. From 1985 to the present, close cooperation with intramural staff has generated 19 contract topics resulting in 101 phase I submissions and 28 awards. Of these, 21 led to phase II proposals with seven awards being made thus far. Three phase II proposals are still under review. During FY-91, 21 grant applications were received under the SBIR program, and six of these were phase II applications. Of these, three phase I (20%) and three phase II (50%) grants were funded. This reflects a much improved success rate, particularly for the phase II conversions.

Figure 1
Extramural Programs Branch



Fiscal Summary: Estimates for FY-91 indicate that 207 grants funded for approximately \$43 million are monitored by the Branch. These grants are distributed among the various grant mechanisms as indicated in Table 1 and in Figs. 2 and 3.

Table 1
Distribution of Grants
Extramural Programs Branch
Epidemiology & Biostatistics Program

<u>Program</u>	<u># Grants</u>	<u>% Total</u>	<u>Estimated Total Cost</u>	<u>% Total Costs</u>
R01	120	58.0	21,731,757	50.8
R03	21	10.2	227,985	0.5
R13	3	1.5	4,000	0.0
R15	1	0.1	0	0.0
R29	16	7.7	1,275,287	3.1
R35	4	2.0	2,692,679	6.3
R37	8	3.9	3,594,460	8.4
R43/44	10	4.9	696,233	1.6
RFA	4	2.0	1,074,732	2.5
P01	14	6.8	11,237,117	26.3
U01	6	2.9	230,765	0.5
TOTAL	207	100.0	42,765,015	100.0

Figure 2

Numbers of Active Grants by Mechanism Extramural Programs Branch, FY91

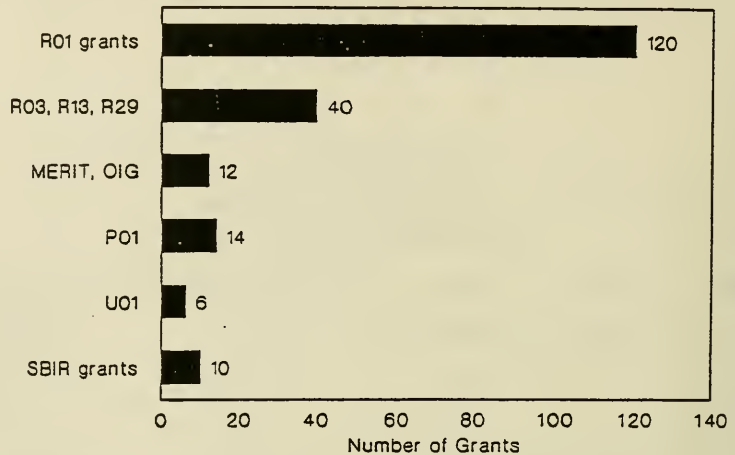
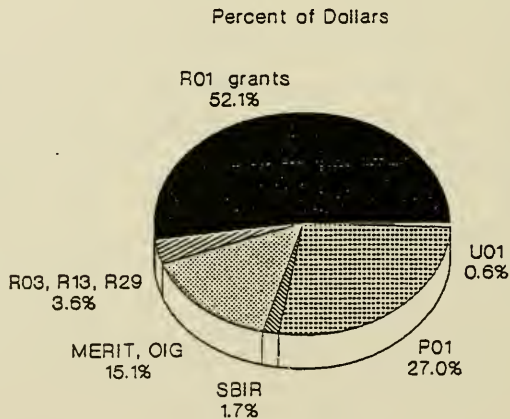


Figure 3

Distribution of Grant Dollars Extramural Programs Branch, FY91



BIOMETRY

Description

The extramural biometry program supports the development of improved statistical methods for the design, conduct, and analysis of biomedical/epidemiologic studies of cancer. The greatest attribute of the program is the ability of biostatisticians to choose interesting research problems arising from the methodological needs of ongoing biomedical research. The process is cyclic; identification and solution of existing problems leads to the recognition of new problems and new solutions. For example, in the field of clinical trial methodology, a need was seen for monitoring committees that, with statistically sound sequential analysis procedures and clearly defined stopping rules, were to be empowered to terminate a study should preset criteria be met. As these procedures were developed and implemented, investigators engaged in clinical trials saw possibilities for utilization of their data far beyond those originally envisioned. Single endpoints gave way to multiple endpoints; data collected over time were seen as providing a means for studying the natural history of disease and the effects of competing risks. Biostatisticians see a need for developing methods to appropriately analyze longitudinally collected repeated measurement data which are affected by problems of correlation, missing values, misclassification, censoring, differing/irregular measures of time, covariates, continuous versus discrete variables, noncompliance, sample size and deviation from asymptotic theory.

The biometry program remains extremely active, although it is a much different program than in the recent past. Most of the current projects are from talented young researchers launching their careers in biostatistics. As a result, this dynamic program is growing in breadth and depth. Many of the projects have been initiated within the past year and have yet to submit their first progress report. Only those investigators able to convince the Initial Technical Review Groups that their research will make new contributions to the literature and provide useful tools for applied biostatisticians and epidemiologists are receiving ratings worthy of support; evidence of a track record, on its own, is not sufficient. Some of the new projects underway include development of new methods for improving cancer risk assessment; exploration of cohort and case-control studies and the use of historical controls to increase efficiency and reduce cost; semi-parametric and non-parametric statistics; mathematical modeling of carcinogenic toxicologic studies; and Bayesian approaches to several new areas in biostatistics.

Research Accomplishments

Clinical Trials: A number of issues associated with group sequential methods for the design and analysis of clinical trials have made it difficult to implement and use them in practice. One such issue involves the implicit assumption that the outcomes of interest (such as remission, death) are immediately available for analysis. In reality, only a subset of the reportable data is available at the time an interim analysis is due. This inherent delay in data availability can seriously disturb the usual group sequential assumptions and can lead to biased treatment comparisons. Statisticians are attempting to develop methodologies which will permit adjustment for the types of delay likely to be seen in practice (185).

Non-compliance in clinical trials is another problem. Subjects are assigned to specific treatment protocols; however, because some may fail to comply with their assigned regimen, a subject's actual treatment may differ substantially from the assigned treatment, diluting the treatment effect. A class of semi-parametric failure time models and use of frailty (random effects) models are being developed for correcting this phenomenon (185,121).

Analysis of repeated measures in clinical trials, epidemiological and environmental studies has received much attention recently (90,137,150,63,92, 9,88,37). In most studies involving repeated measures, the investigator is interested in relating responses to other variables (covariates) under study. There are a variety of methods in the literature for analyzing repeated measures data, but few are suited to data from longitudinal studies where knowledge of the distribution functions are lacking. To assure appropriate analysis of these data, distribution-free methods are being developed. The ultimate goal of one such project is to devise a simple guideline for the selection of distribution-free statistics for particular applications (90).

A response variable repeatedly observed for each participant in a clinical trial is often categorical, such as quality of life measured on a scale of excellent, good, fair, or poor. Usually the major response variable is measured at the beginning of the trial and interest is in the "shift" from time 0 to other time points. The method by McCulloch for a single time analysis of paired ordered categorical data without covariates is being extended to multiple points in time while simultaneously including effects of covariates. This should prove to be a useful tool for practical applications in cancer studies (192).

Carcinogenic Risk Assessment: A number of investigators are addressing the question of how to improve the assessment of carcinogenic risk. A group of researchers using the National Toxicology Program carcinogenic bioassay database is looking at age, length of follow-up and use of data from sacrificed animals in a rigorous systematic manner which should provide useful new knowledge (35). New models should lead to more reliable estimates of risk which are more biologically relevant for toxicology. An important facet will be to strike a balance between biological considerations leading to model complexity and statistical considerations leading to reliable inference (150).

Researchers are continuing to work with the Biological Effects of Ionizing Radiations (BEIR) data to determine carcinogenic risk resulting from various patterns of exposure. There are epidemiological and experimental data establishing the carcinogenic effect of radiation and the dependence of cancer rates on doses and temporal factors such as age at exposure, time since exposure, attained age, and duration of exposure. These observations have potential for delineating mechanisms of radiation carcinogenesis (182,135, 90,19,112,207).

Epidemiologic Methods: An ongoing study on epidemiologic analytic methods has been exceptionally productive over this last grant period. The work has focused on issues such as the analysis of aggregate epidemiologic data, the effects of misclassification on estimates of risk and odds ratios, comparison of logistic regression and discriminant analysis in variable selection, development of inference procedures for matched-pair survivorship data, estimation of confidence intervals around standardized mortality ratios, and

test of homogeneity for sparse data in multiple two-by-two tables. The work has been well received by peers and has made a substantial contribution to epidemiology (202).

A project which has been very productive this year has resulted in multiple publications as well as a textbook. The text defines the Bayesian approach to regression analysis with censored data, and provides a unified presentation of a variety of algorithms for likelihood and Bayesian inference. The intended audience for these publications consists of Ph.D.-level researchers in missing-data methods, Bayesian inference, simulation and computing (179).

Projections

A concern of vital importance to program staff is the lack of enthusiasm on the part of the Initial Technical Review Groups for recommending support for development of portable software and clear documentation of solutions to theoretical biostatistical problems. It appears that there is little appreciation for the fact that most theoretical developments are published in highly technical journals. As a result, there has been an unfortunate delay in the implementation of advances in theoretical biostatistics to epidemiologic research.

To address this concern, a workshop will be held to determine how the biometry program can better meet the biostatistical and computing needs of epidemiologic research. This session will bring together a small group of highly qualified biostatisticians and epidemiologists to consider the problems in depth. Each participant will be requested to present a paper expressing his/her own perception of these problems followed by open discussion. Recommendations for possible mechanistic approaches which may help alleviate the problems will be solicited.

The program is working with some investigators to help them obtain Minority Supplements for well-qualified young black statisticians. In each case, the parent grantee (Principal Investigator) is working to see that the applicant has the best possible opportunity to be successful in research.

EPIDEMIOLOGY

Description

The cancer epidemiology extramural research program supports descriptive, analytic and methodologic studies. Inquiries into the natural history of neoplasia in humans; elucidation of the role of precursor and associated conditions; studies of the incidence, prevalence and mortality from human cancers; and examination of the geographic distribution or time trends are appropriately assigned to this program.

The program is particularly interested in analytic epidemiologic studies of host factors and environmental, occupational or lifestyle exposures, including a number of specific agents known or suspected to influence cancer risk. There is strong interest in supporting research which elucidates causal associations and mechanisms of carcinogenesis in human populations, as well as basic epidemiologic research which may provide information essential to preventive intervention. In this report, the research accomplishments of smoking, diet and nutrition projects will be included under the Epidemiology heading.

Research Accomplishments

Smoking: The incidence rates of most tobacco-related cancers, including cancers of the lung, esophagus, larynx and oral cavity, are higher among blacks than among white Americans. Although blacks are more often current smokers, they smoke on average fewer cigarettes per day than whites. Blacks tend to smoke higher tar, higher nicotine and more mentholated cigarettes than whites.

The program currently supports both prospective and case-control studies to investigate ethnic differences in smoking patterns and the adverse health risks associated with smoking low-tar and/or low-nicotine cigarettes. Data from an ongoing hospital-based case-control study for the period 1980-1990 were recently analyzed to determine whether sociodemographic factors, smoking-related factors, alcohol consumption or body mass index could account for the observed difference in smoking patterns between whites and blacks. The larger proportion of light smokers among black current smokers could not be explained by differences in cigarette preference (tar level, menthol/non-menthol, filter/non-filter), duration of smoking, inhalation practice, timing of the first cigarette of the day, or proportion of each cigarette smoked, nor by other variables, such as age, education level, alcohol consumption, body mass index, or type of hospital. The marked differences in level of smoking between blacks and whites may be due to differences in purchasing power. Another possible explanation which will be evaluated is that there may be differences in the metabolism of nicotine between blacks and whites (204).

The data on the relationship of smoking status and cigarette tar yield to the incidence of lung cancer among a large cohort of San Francisco Bay Area residents aged 30-89 years who completed a tobacco use questionnaire between 1979 and 1986 were recently analyzed. The prevalence of smoking was inversely related to age, higher among men than women, and was highest among blacks, moderate among whites and lowest among Asians. The prevalence of low-tar cigarette use was higher among women than men, and was highest among whites,

moderate among Asians and low among blacks. Age-specific relative risks for lung cancer ranged from 11 to 34 for smokers compared to non-smokers, and from 4 to 7 for former smokers compared to non-smokers. In multivariate analysis assessing the relative risk of lung cancer associated with tar yield and selected cigarette usage characteristics, the frequency of inhalation was the only characteristic for which the association was close to statistical significance (RR=1.4, $p=0.06$). An interesting finding was that the lung cancer risk among former smokers was associated with duration of time since quitting. Although the risk diminished over time, even 15 years since quitting, the risk of lung cancer was almost twice as high among former smokers than non-smokers (46,47).

Seventh-Day Adventists (SDAs) do not smoke by church proscription. However, many are adult converts who smoked cigarettes prior to their baptism into the church. A cohort of 34,000 SDAs completed a census questionnaire in 1974 and a lifestyle questionnaire in 1976. The cohort was followed for 6 years, during which time all incident cancers were detected through annual mailings and record linkage with the two population-based tumor registries in California. In comparison with non-smokers, ex-smokers experienced relative risks of 2.0 for total leukemia, 2.2 for myeloid leukemia and 3.0 for myeloma. Risks increased with increasing number of cigarettes smoked daily and also with the total duration of smoking. These data suggest that cigarette smoking may induce certain hemopoietic neoplasms.

Diet: Epidemiological observations and studies in laboratory animals suggest that cancers of the stomach, colon, pancreas, prostate, breast, ovary and endometrium are associated with dietary factors. Diet has been proposed to influence cancer risk in a number of ways: through effects from undernutrition on the immune system; through exposure to carcinogens as food contaminants; through the formation of carcinogens during the storage, processing or cooking of foods; through carcinogens produced in vivo from ingested food; and through the protective effect of certain dietary components by their influence on carcinogen detoxification systems.

An ongoing multidisciplinary project is elucidating the etiology and approaches to prevention of gastric cancer. This study is being conducted in a very high-risk population in Narino, Colombia, and among patients in New Orleans, Louisiana. The first phase of the investigation was based on cross-sectional studies which identified basic pathologic features and risk factors. The second cycle completed cohort follow-up. Several factors were identified as possible etiologic agents in the development of gastric cancer. These include excess salt, nitrates, Helicobacter pylori in the stomach mucosa, deficient dietary intake of antioxidants, and certain genetic factors that influence susceptibility. These factors act at different stages in the development from normal mucosa to gastric cancer, i.e., superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia, and carcinoma in situ. The research is now focusing on an intervention study to test the causal role of identified factors in the development of precursor lesions. A randomized, factorial, double-blind trial in Colombia will determine effects of the antioxidants, ascorbic acid and beta-carotene, on the pathogenesis of precursor lesions of gastric cancer (33).

Published epidemiological studies have suggested a protective role of beta-carotene for certain epithelial cancers. However, for prostate cancer, in

several case-control studies, an enhancing effect of vitamin A intake, including retinol and carotenoid precursors, has been suggested (53,87). Because of the current interest in beta-carotene as a chemopreventive agent, data from a population-based, case-control study among the multiethnic populations of Hawaii were examined for the main food sources of beta-carotene. Vegetables and fruits containing other phytochemicals were also examined. The main food sources of beta-carotene were carrots, papaya, pumpkin, sweet potatoes, and mangoes. With the exception of papaya, which was positively associated with prostate cancer risk among men aged 70 years and older, consumption of yellow-orange fruits and vegetables, tomatoes, dark green vegetables, and cruciferous vegetables was not associated with prostate cancer risk. The association with papaya was consistent across various ethnic groups, persisted even after adjustment for many potential confounders, and remains unexplained.

Hormone Replacement Therapy: Over the past three decades, large numbers of women have used estrogen therapy to alleviate menopausal symptoms. In recent years, long-term use of estrogen replacement has been advocated for its beneficial effects in osteoporosis and coronary heart disease. Since breast cancer appears to be influenced by length of exposure to endogenous ovarian hormones, exposure to exogenous hormones may also influence the development of this malignancy. Recent investigations have provided some evidence of increased risk. Findings from a prospective study of 20,341 SDA women who used exogenous hormones either as oral contraceptives (OC) or hormone-replacement therapy (HRT) have recently been reported. During the 6-year follow-up period, 215 histologically confirmed primary breast cancers were detected in this cohort. The mean age at diagnosis was 66 years, indicating a primarily postmenopausal case series. In this cohort, current use of HRT was associated with a 69% increase in breast cancer risk, which was statistically significant. However, there was no strong increase in risk with increasing duration of use of HRT. Women who were using HRT in 1976 experienced increased risk in certain subgroups, notably women with a history of benign breast diseases (RR=2.8).

The Nurses' Health Study was established in 1976 to study risk factors for cancer and other diseases, with particular emphasis on the potential effects of exogenous hormones and risk of breast cancer. During 10 years of follow-up, there were 722 incident cases of breast cancer. Overall, past users of replacement estrogen were not at increased risk (RR=0.98), including those with more than 10 years of use (RR=0.70). However, relative risk of breast cancer was significantly elevated among current users (RR=1.36). Among current users, a stronger relationship was observed with increasing age but not with increasing duration of use. Among women who did not consume alcohol, the risk of breast cancer was not increased by current use of postmenopausal hormones. Among alcohol consumers, current hormone users were at increased risk of breast cancer (age-adjusted RR=1.56). This observation needs further evaluation to confirm an interaction between HRT and alcohol (167).

Environment: The most common form of cancer in the white population of the United States is non-melanoma skin cancer. The two principal histologic types are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Due to the low case-fatality rate few epidemiologic studies have been reported. In a prospective study among a cohort of 73,366 nurses in the United States who were 34 to 59 years of age in 1980, and who had no previous skin or other

cancer, a steep increase of BCC with age was observed in the Northeast and Northcentral states as well as the Western and Southern states. The incidence rate of BCC among women 60 to 64 years of age in Florida was more than 1% per year. The age-adjusted RR for BCC was about 50% higher in California and twice as high in Florida than in the Northeast states. Red, blonde, and light brown natural hair colors were all associated with increased risk of BCC, relative to having dark brown hair. Black hair tended to be inversely related to risk. There was a positive association in a dose-response manner both with tendency to sunburn as a child or adolescent and with lifetime number of severe and painful sunburns on the face or arms. Tendency to tan was associated with decreased risk. Cigarette smoking did not alter the risk of BCC (167). The chief established risk factor for BCC is ultraviolet sunlight exposure. A reason for concern about an increasing incidence of this cancer is the potential for increased ultraviolet exposure due to depletion of the stratospheric ozone layer from chlorofluorocarbon emissions. It has been estimated that each 1% decrease in ozone concentration will increase the incidence of non-melanoma skin cancer by 1 to 3%.

Dysplastic nevi (DN) are precursors for malignant melanoma. The results of a clinic-based case-control study of DN were recently published. DN cases were younger and better educated than controls. Sun sensitivity, assessed by reported depth of tan after multiple exposures, was associated with both DN and melanoma risk after controlling for age and education, but the risk was nonlinear for DN. Indicators of actual sun exposure, such as time spent in summer midday sun, were not associated with DN risk, after controlling for age and education, whether or not depth of tan was controlled in the analysis. These observations suggest a trait linked with sun sensitivity in the development of DN (194).

Projections

Well-designed epidemiologic studies focusing on the cultural and genetic heterogeneity of U.S. population subgroups are needed to seek out clues to lifestyle factors, other environmental exposures and susceptibility states that may contribute to cancer risk. The Branch issued an RFA to stimulate research on the "Epidemiology of Cancer in U.S. Minority Populations." Fifty-four proposals were received in response to this announcement. It is anticipated that 7 or 8 awards will be made following the National Cancer Advisory Board (NCAB) review in September 1991. Incidence rates for certain cancers exhibit a progressively upward trend with advancing age. Workshops are being planned to discuss the age pattern for several cancers to develop new initiatives for targeted epidemiologic research which may provide insights into the role of cumulative environmental exposures, latency periods, multi-stage mechanisms, and intrinsic susceptibility associated with the aging process.

GENETIC EPIDEMIOLOGY

Description

The genetic epidemiology program supports projects which study the interaction between somatic and germinal genetic alterations and exogenous factors in the etiology of cancer in humans. Projects supported by this program focus on the analysis of genetic susceptibility for various tumors in high-risk populations, and on the study of other risk factors in familial clusters of cancer-related diseases. An increasing number of these projects are using sophisticated molecular techniques to identify and map genes or gene markers related to the particular type of cancer under investigation. Several recent and exciting advances in the identification of chromosomal and gene loci associated with increased risk of cancer have been achieved by investigators supported by this program.

During the last year, particular emphasis has been placed on the study of breast and colon cancer because of recent advances in the molecular and genetic epidemiology of these tumors and their public health importance. Much effort is now focused on the identification of heritable precursor lesions leading to these tumors, to provide etiological clues and preventive approaches. Other forms of cancer currently studied within the program are childhood sarcoma, glioma, melanoma, lung cancer and Wilms' tumor. Inherited conditions that predispose to cancer, such as ataxia-telangiectasia and Li-Fraumeni cancer family syndrome, are examined as well.

In addition, a component of this program deals with developing statistical models for considering polygenic modes of inheritance, environmental risk factors, and gene-environment interactions. This includes the development of practical computer programs that allow analysis using standard packages, and simulation studies of the performance of these new methods to compare them with more standard methods.

Research Accomplishments

Breast cancer has long been recognized to be a familial disease. The hypothesis of a rare breast cancer susceptibility allele that is dominantly inherited has been supported by several studies. Multidisciplinary studies, partially or entirely supported by the genetic epidemiology program in 1990-91, have offered new clues for our understanding of malignancies in general and breast cancer in particular.

A California group performed genetic linkage analysis of 23 families with a high risk for early onset of breast cancer (e.g., breast cancer occurring under 46 years of age) using as a marker an anonymous polymorphic DNA sequence defined by the probe CMM86. Results have shown evidence of tight linkage to a locus on the long arm of chromosome 17 (q21). When families with a progressively older mean age of onset are added to the series, linkage becomes weaker and ultimately disappears. This supports the hypothesis that familial breast cancer is a genetically heterogeneous disease, and that the early onset pattern identifies a major subgroup that can be attributed to a gene located at 17q21. Several candidate cancer genes have been mapped to this region of chromosome 17: the oncogene ERB-B2 (known to be amplified or overexpressed in a proportion of breast cancers), two growth hormone genes, the human homologue

of the mouse mammary tumor virus integration site, the gene for nerve growth factor receptor and for the retinoic acid receptor, the homeobox sequence involved in tissue differentiation and organogenesis, the gene for a protein kinase implicated in cell activation, and the NM23 tumor suppressor gene, which has recently been found to play an important role in tumor metastasis. However, the identity of the putative breast cancer gene is not yet known. Future work will be aimed at identifying its precise location, and at trying to find out whether different genes are implicated in early and late-onset form of the disease (83).

Since breast cancer etiology cannot be entirely explained by a single or simple mode of inheritance, and the breast cancer phenotype may involve substantial genetic heterogeneity, the goal of localization of susceptibility genes cannot be attempted without consideration of the nature of gene-environment interaction. This approach is being taken by a group using statistical models that take into consideration both genetic and environmental risk factors in estimating the parameter of linkage of DNA markers with gene loci suspected to be etiologically related with the development of breast cancer. The project studies 442 families in which the index case has bilateral breast cancer diagnosed before fifty years of age (61). It is also being used to develop analytical techniques informative for analyzing gene-environment interaction data. The investigators have used the affected-pedigree-member method (APM) to conduct linkage analyses on 19 pedigrees in which the proband had premenopausal bilateral breast cancer. Non-independent segregation between 14 standard genetic markers and breast cancer was evaluated. A premenopausal cases-only and an all-cases analysis were conducted. A non-independent segregation for the red blood cell antigen C3 and ESD was observed in the premenopausal cases-only analysis but not in the all-cases analysis. This result is consistent with the hypothesis that the etiology of premenopausal breast cancer is different from the etiology of the postmenopausal breast cancer. The APM method presents several advantages over the more traditional lod score method: it does not need any assumptions about the underlying mode of inheritance and it obviates the need to incorporate environmental exposures into the analysis since it is limited to affected members whose exposures, whatever they were, were sufficient to produce the disease (183).

A comprehensive review of anatomic risk factors for breast cancer has been performed by another group. Five percent of the women who underwent biopsy in the pre-mammographic era had specific patterns of atypical hyperplasia (AH) that approached the criteria of carcinoma in situ, which is considered a true precancerous lesion because of its regular association with recurrence at the site of its initial diagnosis. These women had a risk of cancer four or five times that of the general population; further studies indicate an appreciable interaction between AH and other non-anatomic risk factors, particularly a family history of breast cancer.

Following this lead, researchers have modified the standard technique of fine needle aspiration to screen for the presence of proliferative breast disease (PBD) in women at high risk for breast cancer but with no clinically apparent abnormalities. A study of PBD and breast cancer in 103 women of 20 kindreds (selected for the presence of two first degree relatives with breast cancer) and 31 control women indicates that PBD is a significant risk factor for the development of breast cancer, and appears to be a precursor lesion for this

tumor. Cytologic analysis of four-quadrant fine needle aspirates revealed that 35% of clinically normal female members of the 20 breast cancer kindreds examined had PBD, compared with 13% of controls. Pedigree analysis of the 20 kindreds strongly rejected the sporadic model in favor of a genetic etiology, whether breast cancer was analyzed alone or breast cancer and PBD were considered as a combined trait. The most parsimonious model suggests that a highly penetrant dominant susceptibility locus is responsible for a considerable portion of the cases of breast cancer. It has been suggested that most breast cancer arising in high-risk families is expressed as premenopausal and/or bilateral breast cancer. In these particular kindreds, a slight majority of breast cancer onset was post-menopausal and only 8% of the cases were bilateral. Seemingly benign lesions have been identified as precursors for other tumors. If future studies will demonstrate that PBD can truly be considered a premalignant state for breast cancer, this could constitute a further confirmation of the widely accepted theory that several genetic events are needed for progression to cancer. Further, it would indicate that the predisposition to the precursor lesion, in the form of a gene that gives rise to PBD, is much more common than was previously thought (165).

A recent landmark finding contributing to the understanding of cancer in general, including breast cancer, concerns p53, a gene located on the short arm (p) of human chromosome 17, and coding for a 53kd nuclear protein. The normal gene functions as a tumor suppressor. Mutations of one copy of p53 and/or deletion of the normal gene are common in many human cancers, including breast tumors. An inherited mutation of p53 has, in fact, been discovered in the Li-Fraumeni cancer family syndrome, a rare condition characterized by the familial occurrence of diverse early-onset malignant tumors. The pattern of tumor inheritance of these syndromes is compatible with autosomal dominant expression of a single gene with incomplete penetrance (174). Compelling data reported by two groups, including investigators supported by this program, show that five Li-Fraumeni families bear germ line point mutations of p53, all clustering within a highly conserved region of the gene and similar to somatic mutations already recognized in tumor cells.

Colon carcinoma is the second leading cause of death due to cancer in the United States. Because genetic factors are thought to contribute substantially to the pathogenesis of about 10% of the cases of colorectal cancer, it is important to have a better understanding of these genetic components. The Utah population database, which consists of genealogic data combined with state registry cancer records, has been used to examine the clinical feature of all cases of colon cancer in this well-defined population. Colon cancers were found to cluster excessively in families, with no association of familial clustering with proximal or distal location of the tumor or age at onset (165,25).

A specific genetic condition, familial adenomatous polyposis coli (FAP), defined by the presence of more than 100 visible adenomatous polyps in the colon by the end of the second or third decade of life, is considered a precursor condition for the early development of colon adenocarcinoma. The hypothesis that inherited factors play a role in the development of sporadic adenomatous polyps and colorectal cancers derives from the observation that both conditions frequently exhibit a familial tendency, often in combination with one another (165,25).

Recently, the gene responsible for FAP was mapped to the long arm of chromosome 5 by means of polymorphic DNA markers. Genetic linkage studies with seven polymorphic DNA markers linked to the FAP locus region were performed on a large kindred with a history of colorectal cancer of early onset. The great majority of the members of this family did not meet the criteria for the diagnosis of FAP, but many had a smaller number of colonic polyps (2 to 40). To improve the chance of successful linkage, those designated as affected were those with clinical features least likely to appear in the general population by chance, including individuals with five or more adenomatous polyps. Results of linkage analysis demonstrated that the genetic defect responsible for the predisposition to polyps and cancer of the colon in this kindred is located on the long arm of chromosome 5 at or very near to the site of the mutation responsible for FAP. However, the mutation found in this study seems to differ from the mutant allele responsible for classic FAP, in that subjects who inherited the responsible allele generally had a number of polyps ranging from 1 to 100. This wide variation in phenotypic expression could be explained by a diversity of FAP alleles combined with the influence of other genes and/or environmental differences. These results strengthen the hypothesis that a significant fraction of so-called "common" colon cancer (other than the tumors associated with FAP, Gardner's syndrome and familial nonpolypotic colorectal cancer) arises in part on the basis of inherited susceptibility. Further linkage studies leading to an identifiable genotype will allow accurate studies of diet-gene interaction for colon polyps and cancers, and also will likely be useful in directing colon cancer screening efforts (25).

Families with a high incidence of cutaneous melanoma (CM) have been described in which melanoma co-segregates with multiple atypical moles, known as dysplastic nevi. Linkage studies of families displaying both melanoma and the dysplastic nevus syndrome (DNS) have yielded conflicting results. The previously reported linkage between CM and DNS to markers located on chromosome 1p36 was examined in three Utah kindreds ascertained for multiple cases of CM. Family members in these kindreds were genotyped for the two markers reported to be most closely linked to these phenotypes. Analysis of melanoma alone and of a combined melanoma/DNS phenotype showed no evidence of linkage in these families. Alternate explanations for this discrepancy include diagnostic and/or genetic heterogeneity. Diagnostic uncertainty in the DNS phenotype, especially with regard to use of histopathological analysis, remains a controversial issue. Research is in progress to ascertain whether two quantitative nevus phenotypes that can be measured objectively can be more reliably used for genetic analyses in the Utah kindreds (164).

Ataxia-telangiectasia (A-T) is an autosomal recessive syndrome characterized by progressive neurologic disorder, immune dysfunction, excessive sensitivity to ionizing radiation, and a striking predisposition to cancer. The A-T gene, localized on chromosome 11q, also has effects in heterozygous individuals, who constitute approximately 1% of the United States population. Studies from an NCI-supported group have shown that the A-T heterozygote has a 2- to 3-fold excess risk of cancer at all sites, a 5- to 7-fold risk for cancer of the female breast, and an overall 2- to 4-fold risk of excess early adult mortality. A recent study of 44 affected families has provided supportive evidence for the association of cancers with A-T heterozygosity, and yielded further insight on which specific type of cancer might be associated with heterozygosity of the A-T gene. As in the largest study published, breast

cancer was the most frequently occurring cancer in this group of A-T families. An excess number of lung, prostate and pancreatic cancers, melanoma, lymphoma and lymphocytic leukemia compared to the expected values was observed. An observed deficit of cancers of the colon and rectum in these families is consistent with earlier findings, and suggests that these particular cancers are not associated with A-T heterozygosity. In seeking the most efficient strategy to use molecular methods to assess gene-disease association in the case of A-T gene and cancer, this group of investigators developed a new "index test" technique. This statistically powerful method can be used to test any hypothesized association between a candidate allele for which there is a specific laboratory test and a common chronic disease. Using this procedure, results are unlikely to be influenced by confounders, systematic bias, or genetic heterogeneity (178).

Human gene mapping studies present several difficulties that are due to the amount, complexity and diversity of the data, and also to the absence of a systematic and optimal experimental strategy. To provide a link between data, analysis programs and the gene mapping experiment, NCI-supported investigators developed a gene mapping expert system (GMES). The first role of GMES is to provide a dynamic representation of the experiment in progress: this makes it possible for the users to explore the state of the experiment at any time. Next, GMES focuses on planning genetic marker selection by suggesting optimized sets of markers to the user who makes the final selection. Finally, once the interfaces to the database and statistical programs are completed, GMES serves as a link between the data, the analysis programs and the experiment itself. As amplified sequence polymorphisms have become powerful genetic markers, the system needs to be expanded and adapted to this new class of genetic markers. The prototype GMES is a flexible template, which can be used as a framework for a fully automated genetic analysis system (165).

Perhaps the most difficult task in the pursuit of detailed knowledge of the human genome is the identification of chromosomal regions containing specific genes or gene clusters responsible for significant polygenic variation of a quantitative trait. In humans, most previous efforts at linkage of quantitative traits having significant phenotypic effects have used the "sib pair" or "sibship" methods.

A unique method for analyzing specific genetic components involved in the determination of human quantitative multifactorial traits has been devised by a Utah group. At any given locus on a chromosome, two siblings can share either zero, one or two genes identical by descent. The method estimates the proportion of genetic material shared by sibling pairs in a specified chromosomal region, based upon their marker genotypes at a set of marker loci spanning the region. These estimates are used to partition the genetic variance of a quantitative trait to specific chromosomes or chromosomal regions. Simulation techniques have shown that this method is more powerful than existing methods of quantitative linkage analysis based on sib pairs. Further work is necessary to examine the robustness of the method to departures from its idealized model (165).

Projections

This is a very vital program that has received new impetus from the recent technological and theoretical advances in the molecular and cellular biology of cancer. Research is supported by the full range of available grant mechanisms, and outstanding results have been obtained by the currently funded program projects (P01) both in terms of cross-disciplinary scientific advances and translation of results into practical applications (GMES is an example of the type of development made possible by the P01 mechanism). New grants funded in the past year include a study on the long-term follow-up of Wilms' tumor survivors to elucidate the genetic origin of this tumor (20), a project focusing on the development of new statistical models for genetic epidemiology (183), and an investigation of the familial factors associated with malignant glioma (203).

In future years, research pursuing the identification of women at high risk of breast cancer due to genetic, environmental and anatomic factors must be a priority, as such research will lead to early diagnosis and prevention of a tumor that constitutes a considerable public health problem. Efforts will also be made to expand research on the genetic epidemiology of prostate and ovarian cancers.

Multicenter collaboration is critical to the progress of this type of research, because working with large (hence informative) cancer families is a costly and lengthy enterprise, and because the collaboration of multidisciplinary teams including genetic epidemiologists, clinicians and basic scientists is needed increasingly to encompass the full scope of molecular genetic/epidemiology research. The use of more creative mechanisms of support, such as cooperative agreements, and appropriate review teams responding to the particular characteristics of these applications, will facilitate future development and contribute to creating a network and sharing the resources needed.

Efforts will be made to promptly translate new epidemiologic and mechanistic findings into prevention strategies, with a careful eye to ethical aspects of genetic screening. With this purpose in mind, it is also vital to maintain constructive collaboration with programs having overlapping interests both within and outside NCI. In this spirit, a planning meeting has been held with representatives from the Division of Cancer Etiology Board of Scientific Counselors, NCI-supported genetic epidemiologists, and representatives of other interested programs within and outside NCI, as the first step toward the organization of a state-of-the-art Genetic Epidemiology Conference and a grantees workshop.

BIOCHEMICAL/MOLECULAR EPIDEMIOLOGY

Description

The biochemical epidemiology component of the Branch has fostered development and application of laboratory methods specifically for epidemiologic studies of cancer etiology. Funding support has been provided by cooperative agreements (55,77,79,96,162,187), investigator-initiated and program project grants (31,56,116,118,120,130,146,168,180), and the Small Grants Program (94,169,171). Of greatest interest have been the efforts focused on identification and validation of useful biomarkers reflecting host susceptibility and/or exposure to carcinogenic agents. Progress during the past year includes: adaptation of innovative laboratory tools to measure human exposure to dietary carcinogens, radiation, and environmental genotoxins; comprehensive validation of tests which assay cytochrome P450IA2 and N-acetyltransferase enzyme activities; technological improvements in DNA adduct analyses; and evaluation of enzymatic and cytogenetic markers of susceptibility to breast and aerodigestive cancers.

Research Accomplishments

The role of dietary factors in the pathogenesis of colorectal cancer and other neoplasms of the gastrointestinal (GI) tract has yet to be elucidated. Although evidence has shown diet-related processes can affect carcinogen exposure of the mucosa and other organs, in situ measurement or monitoring in humans has not been possible. In addition, there have been no methods to characterize dietary components or potentially genotoxic substances within the GI tract. A novel non-invasive tool for identifying GI carcinogens, a semi-permeable and magnetically-retrievable microcapsule, has been developed and satisfactorily tested in animals and human volunteers. Experiments have shown that the microencapsulated targets are reproducibly responsive to electrophiles, N-nitrosating and cross-linking agents, and reactive oxygen species. They also have the capacity to detect modulating effects by dietary fiber and beef protein on carcinogen pharmacokinetics and DNA adduct formation. These capabilities coupled with a close correlation to DNA-damage assays indicate potential usefulness in studies of dietary risk factors and cancer development (120).

Another innovative approach for assessing in vivo somatic cell mutations is the "BR6" assay. This method, performed on a single-beam flow cytometer, utilizes monoclonal antibody labelling specific for M and N allelic forms of the red cell-surface protein glycophorin A (GPA). Variant cells which lack binding of one antibody are presumed to represent gene-expression loss mutations. Variant frequencies, a measure of genetic damage, are elevated in individuals exposed to ionizing radiation, genotoxic agents, or those with inherent susceptibility to mutations. Although technical aspects of the BR6 assay lend suitability to large-scale studies of human populations, the reproducibility and sensitivity of the assay to varying environmental exposures must be ascertained. Comparison testing with HPRT, HLA, and Hb somatic cell mutation assays demonstrate complementarity, thus suggesting the possibility of multiple endpoint analyses for biodosimetry and cancer risk assessment (77).

Caffeine metabolites in urine can be used to estimate activities of three hepatic enzymes: cytochrome P450IA2, a catalyst of pre-carcinogen conversions to carcinogens; N-acetyltransferase (NAT), a polymorphic enzyme used for acetylator phenotyping; and xanthine oxidase, a major source of active oxygen species. All are of interest in studies of carcinogenesis, and are particularly attractive as potential functional biomarkers for assessing cancer susceptibility among population groups. For example, an association has been observed between genetically low NAT activity and incidence of arylamine-induced bladder cancers. Extensive population studies in human volunteers have been conducted recently to validate and assess the limitations and reproducibility of caffeine metabolic ratio analyses. Demographic and lifestyle factors did not influence the range of variability. Interestingly, nonsmokers had the highest cytochrome P450IA2 activity when compared to smokers among 178 healthy subjects. This would imply only a minor influence of cigarette smoke upon enzyme activity; however, this study was not able to consider confounders or effects of other environmental or genetic factors. In another series of experiments, complete concordance between caffeine acetylator phenotyping and the conventional sulfamethazine acetylation test validated caffeine as a marker for NAT activity in determining acetylator status (79).

Projections

The past year has witnessed many laboratory efforts to produce tailored assays for future large-scale population studies. Validation testing is now in progress, while rapid growth of molecular technology promises exciting prospects for continued laboratory advances. A planning workshop to discuss current research status and future research directions will be held in October 1991. It will take place at a multidisciplinary international conference, "Biomonitoring and Susceptibility Markers in Human Cancer: Application in Molecular Epidemiology", which is being coordinated by the International Agency for Research on Cancer and supported by NCI.

VIRAL EPIDEMIOLOGY

Description

The viral epidemiology program emphasizes the epidemiologic study of risk factors and mechanisms for the development of malignancies associated with human papillomaviruses (HPV) and hepatitis B virus (HBV). The overall objective of the program is to establish the incidence, natural history, and risk factors for malignancies and premalignant conditions associated with viral infections. Of particular interest are studies on the effects of viral strain variation, co-infections with multiple viruses, genetic factors, immune alteration, anti-viral treatments and environmental exposures on the development and progression of virus-associated neoplasia.

Areas of major research activity during the past year have been the study of the associations between HPV infection with invasive and intraepithelial neoplasia of the cervix, and the study of HBV and genetic factors in the development of primary hepatocellular carcinoma (PHC).

Research Accomplishments

Hepatitis B Virus: A preliminary study of familial inheritance patterns was conducted in an Alaskan native cohort of HBV carriers and PHC cases. Beginning with 48 index cases of PHC, family histories and HBV surface-Ag status were obtained from 26 cases and 357 unaffected relatives. HBsAg-positive individuals comprised 89% of the cases and 34% of unaffected relatives. Regressive models of Bonney were used to fit the data for the observed familial aggregation. The best model was that which included a major locus and HBV infection. Heterozygotes for the susceptibility gene with concurrent HBV infection were more likely to develop PHC at a younger age. Both HBV carriers homozygous for the non-susceptibility allele and HBsAg-negative heterozygotes were not at increased risk. The investigators concluded that these results are consistent with their recent report of loss of heterozygosity of 4q in HBV-associated PHC. They further hypothesize a model of oncogenesis whereby PHC risk may be determined by HBV infection and inheritance of a tumor suppressor gene (97).

Human Papillomavirus (HPV): Research activity has continued to profile the prevalence of HPV types in adult women and children using polymerase chain reaction (PCR) technology and serological determinations. According to results obtained from enzyme-linked immunosorbent (ELISA) assays, a statistically significant difference was noted in reactivity of sera to HPV-6bL1 peptide among hospitalized children (44%) versus sexually transmitted diseases (STD) clinic patients (67%). No difference was noted in the comparison of a student clinic population and the STD clinic patients. Additional testing for IgG antibodies to HPV-encoded proteins also demonstrated higher reactivity to HPV-16 in the same clinic patients (54%) as compared to the children (40%). The unexpected high seroprevalence among children suggests sexual transmission is not the only mode of HPV acquisition (104).

In addition to ascertaining prevalence rates in the general population, a major objective of the program is to understand the natural history of HPV

infection with subsequent progression to malignant transformation. Laboratory and epidemiological investigations continue to address this question. In vitro cultures of HPV-16 and HPV-18 immortalized keratinocyte cell lines have displayed karyotypic abnormalities with subsequent conversion to poorly differentiated squamous cell carcinomas; it is hypothesized that HPV transforming genes are responsible. Currently, an ongoing cohort study of women attending an STD clinic has reported an approximate fourteen-fold excess risk of HPV cervical infections (mainly types 16 or 18) associated with cervical intraepithelial neoplasia (CIN) levels 2 or 3. Early age of first intercourse appears to be a cofactor whereas age, number of sexual partners, smoking status, history of STD, and oral contraceptive use are not influential. In a case-control study, repeated colposcopic examinations were performed in a group of women selected randomly from an STD clinic population. Approximately 50% of HPV-negative patients at the first study visit demonstrated colposcopic changes characteristic of HPV presence. A one-year follow-up revealed that HPV DNA could be detected in 41% of these individuals. Another study was designed to characterize the association of HPV infection with condyloma acuminatum, a benign anogenital neoplasm possibly related to subsequent development of squamous cell carcinoma. Southern hybridization and PCR analyses revealed 93.9% of tissue biopsies as HPV DNA positive. Of these the majority (67%) were HPV-6, while the remaining types were either HPV-11 or HPV-16. There was no evidence of multiple HPV infections (69,104).

Projections

The area of HPV research continues to be productive, particularly in the confirmation of type-specific associations with malignant lesions. Substantial progress has also been achieved in the characterization of the immune response to HPV infection. It is anticipated that epitope mapping will advance serological capabilities and, in turn, allow molecular tracking for studies in pathogenesis.

RETROVIRAL AND HIV-RELATED EPIDEMIOLOGY

Description

The retroviral and human immunodeficiency virus (HIV)-related epidemiology program supports studies on the epidemiology, etiology, and natural history of retroviral and HIV-associated cancers and their classic, non-HIV associated forms. The overall objective of this program is to determine the incidence, prevalence and time trends for the occurrence of HIV-related malignancies; to study the etiologic mechanisms for the development of HIV-associated cancer; to define the immunological, virological and environmental risk factors for cancer in HIV-infected individuals; and to clarify the role of retroviral and viral co-infection in the development of the neoplasia.

Molecular epidemiologic studies of malignant processes in HIV-infected individuals include research on potentially carcinogenic viruses, such as human papillomavirus (HPV), Epstein-Barr virus (EBV), and human herpes simplex virus type 6 (HHV-6), in HIV-infected individuals. Other areas of interest are the epidemiology of human retroviruses, such as HTLV-1 and HTLV-2, and the development of statistical modeling of the AIDS epidemic and AIDS-related neoplasms.

During the past year this program has grown considerably, and now supports a wide range of national and international research projects studying retrovirus-associated malignancies in humans. However, most projects are in their first or second year and are still in the data-collection phase. The full range of assistance and procurement mechanisms are used within the program, including an intra-agency agreement with the National Institute of Allergy and Infectious Diseases (NIAID), partially supporting the Multicenter AIDS Cohort Study (MACS).

Because of the worldwide distribution of the AIDS epidemic, the differences in natural history at different geographical locations, and the endemicity of human retroviruses in particular areas, the program also supports a few international studies (1,85,115). Record linkage of the cancer and AIDS registries in the San Francisco area has established a model for baseline estimates of the spectrum of cancers associated with AIDS or with HIV-positive individuals and the evaluation of risk factors (152).

Recent research has specifically focused on the study of the time trends and risk factors for non-Hodgkin's lymphoma (NHL) in representative populations of HIV-infected individuals (such as homosexual and bisexual men and hemophiliacs) and on molecular and clinical epidemiology studies of HIV-associated and classic Kaposi's sarcoma (48,68,95,115,139,209,215,216). The investigation of the role of HIV-HPV co-infection in the development of cervical and anal neoplasia has been supported with national and international studies (1,84,85,127). Finally, we have supported the development of backcalculation techniques for projections of the incidence of some AIDS-related cancers (21,101).

The "First Meeting of AIDS Principal Investigators" supported by the retroviral and AIDS-related epidemiology program was held on March 7 and 8, 1991, in Bethesda. The meeting, in addition to providing a comprehensive scientific update and assessment of the progress of ongoing research within

the program, greatly contributed to an increase in communication, collaborations and sharing of resources among the extramural investigators. It also provided an opportunity for scientific exchange between extramural and intramural investigators. A booklet containing the abstracts of the presentations will be published in the near future.

Research Accomplishments

HIV-associated Malignancies: Research within this area has primarily focused on the study of AIDS-defining cancers, NHL and Kaposi's sarcoma. The most recent analysis performed on data obtained from MACS patients from 1984 to 1990 has shown a significant increase in the incidence of AIDS-defining cancers within this cohort. This is principally due to a sharp increase in the incidence of NHL in this population, as the incidence of KS in the MACS population has shown only a very slight increase. In contrast, the incidence rate of some other opportunistic infections, such as pneumocystis carinii pneumonia (PCP), has been steadily declining since 1987. It is conceivable that the increased availability of zidovudine (AZT) and aerosolized pentamidine prophylaxis is influencing in an opposite manner the frequency of the occurrence of malignant and non-malignant AIDS-defining events. The maturity of this cohort, the wealth of data currently available, and the evidence for changing clinical manifestations of late stage HIV infection, provide the potential for unique and challenging future research (209,215,216).

Individuals infected with HIV have an increased incidence of high-grade B-cell lymphoma. Although the clinical and pathological characteristics of HIV-related lymphomas have now been well described, the etiology of these tumors remain unresolved. Initial hypotheses included the potential association with prior infection by EBV, which has been found in approximately 50% of the AIDS-associated NHL. Previous serologic data have demonstrated that more than 90% of HIV-infected individuals are also EBV-infected, and that reactivation of the EBV infection may be a common occurrence. HIV-infected patients are also at increased risk for developing a persistent generalized lymphadenopathy (PGL), and the presence of immunoglobulin gene rearrangements in approximately 20% of these reactive lymph nodes suggests that PGL may be a precursor state for the development of lymphoma. A recent investigation looked at the presence of EBV in PGL lymph node biopsies of 16 non-HIV infected patients and 35 HIV-infected patients, to determine the possible relationship between EBV-related lymphoproliferation and the risk of malignant lymphoma. The investigators used PCR and *in situ* hybridization techniques to enhance the sensitivity of EBV detection. EBV DNA was not detectable in any of the 16 benign lymph node biopsies from normal individuals, but could be detected from 13 of 35 PGL biopsies. EBV positivity was significantly associated with the concurrent presence of EBV-positive NHL at another site, or subsequent development of EBV-positive lymphoma. Therefore, the detectable presence of EBV DNA in benign PGL biopsies was found to be a significant risk factor for the development of EBV-positive HIV-associated NHL; studies on larger at-risk populations may shed more light on the exact biological mechanism responsible for this association (95).

A distinctive feature of HIV-related NHL is its aggressiveness and poor response to chemotherapy. In an attempt to identify the biological basis for

collected from MACS participants. DNA-content analysis showed that the median proliferative activity of AIDS-associated high-grade NHL was higher than that of high-grade NHL unrelated to AIDS, although this difference did not reach statistical significance. Larger studies will be helpful in determining the prognostic significance of flow cytometric DNA analysis in patients with concomitant HIV infection and NHL (209,215,216).

Human Retroviruses: Human T-cell lymphotropic virus type 1 (HTLV-1) is recognized chiefly as the etiologic agent of human adult T-cell leukemia/lymphoma (ATLL), a disease that is endemic in southern Japan, central Africa and the Caribbean basin, and it is also associated with tropical spastic paraparesis (TSP). The identification of serological markers that are associated with transmissibility of human retrovirus infection is important for planning preventive strategies. An ongoing study supported by this program consists of the prospective follow-up of the adult populations of two HTLV-1 endemic villages in the Mizayaki prefecture of southern Japan, to ascertain their risk of infection with HTLV-1 by sexual exposure. The investigators have evaluated a variety of measures of viral status among married couples who are discordant for carrier status, in comparison with similarly aged couples in which both partners are infected, and a third series of couples where seroconversion was observed. This population has been prospectively followed since 1984, with clinical, serological and interview information collected annually. HTLV-1 tax gene protein is a specific transcriptional activator of the HTLV-1 long terminal repeat sequence (LTR) and is essential for the replication cycle of the virus. Since HTLV-1 tax protein can enhance replication of HTLV-1 virus itself and can stimulate proliferation of lymphocytes harboring virus through activation of some cellular genes, it could conceivably be associated with viral transmission. The investigators used a recombinant tax protein to analyze the relationship between sexual transmission of HTLV-1 and the presence of anti-tax antibodies in these three groups. A suggestive correlation was found between the presence of anti-tax antibody in male HTLV-1 carriers and a high risk of viral transmission via heterosexual transmission to their spouses (114).

HTLV-2 has been sporadically isolated from patients with cancer and from some individuals without evidence of malignancy. Recently, widespread infection with this retrovirus has been reported among intravenous drug users. HTLV-2 positivity has not been clearly associated with a particular human disease, but it has been described in a patient with chronic T-lymphocytic leukemia. The incidence of infection with this virus is quite low, and until recently, no population with endemic HTLV-2 infection had been described. Evidence has now been provided for endemic infection with HTLV-2 in the American Indian population of New Mexico. Data from blood donors suggest that between 1% and 2% of the Indians with no previously known risk factors for HTLV infection have been exposed to HTLV-2. However, no increased rates of hairy-cell leukemia, mycosis fungoides or chronic lymphocytic leukemia have emerged from a study of patients from the New Mexico tumor registry. Research is presently supported to perform a larger, blinded survey to collect seroprevalence data in this endemic population (65).

Statistical techniques and models have been particularly useful in estimating the incidence and prevalence of HIV infection, and in tracking and projecting AIDS incidence. The method of backcalculation, used for projecting AIDS incidence, has been refined during the last year. An important extension

includes statistical methods to account for new infections; it was found that new infections have a relatively small effect on AIDS incidence because of the long and variable incubation period. Methods have been developed to estimate current and future numbers of individuals in different stages of the natural history of HIV infection, thus estimating the number of individuals that could most benefit from HIV treatment. Methods were also developed to analyze cohort data for estimating the AIDS incubation period distribution and were applied to hemophiliac cohorts. A new adaptation of the Poisson regression method for estimating the reporting delay distribution is capable of identifying the main sources of heterogeneity (risk group, geography, calendar trends) in estimating reporting delays. An analysis of sexual partner studies for identifying covariates that increase the risk of transmission of infection is now in progress (21).

Projections

During the last year, the program has acquired cohesion with the funding of new grants and the establishment of a network among supported investigators. Questionnaires are now shared among the investigators interested in HIV and HPV-related research, increasing the feasibility of across-study analyses.

An area of research priority for the next year is the study of the epidemiology and natural history of neoplastic complications associated with HIV infection and AIDS in women and children. This program is part of a PHS-wide women and AIDS working group, and a conference on these issues is planned for FY-92.

SMALL BUSINESS INNOVATION RESEARCH (SBIR) PROGRAM

Description

During the eighth year of the SBIR program at NIH, grant submissions have continued to increase gradually. Within the Branch, the Phase I funding rate has risen to 20%, and successful conversion to Phase II has jumped to 50%. The SBIR contract mechanism has fared better, with a Phase I funding rate of 67% and conversion to Phase II approaching 60%. The Small Business Innovation Development Act of 1982 established the SBIR program in all Federal agencies with research and development funds exceeding \$10 million per year. The mandated set-aside for SBIR awards amounts to 1.25% of the R&D budget in any given year through FY-93. The goal of the program is to promote the participation of small businesses, especially disadvantaged and minority-owned, in Federal research, and subsequent commercialization of any resultant products. Successful projects follow a triphasic course: a six-month feasibility study not to exceed \$50,000 total cost, an intensive developmental effort of up to two years not to exceed \$500,000 total cost, and a final privately-funded commercialization period. During FY-91, the NCI spent \$21.4 million on the SBIR program. Following the trend set in previous years, all the projects funded in the Branch, six grants and three contracts, involve the development of software packages. The nature of software development lends itself well to the SBIR limitations on time and funds.

Research Accomplishments:

Of ten SBIR grants, active during FY-91, four Phase I grants have recently terminated. Of these, three were microcomputer software feasibility studies and one (170) was concerned with designing a hand-held coulometric detector for breath carbon monoxide. The software projects involved a modular clinical trials analysis and management program (102), an indexed oncology research question/answer/reference database (8), and an integrated modular telephone interview package (41). Several Phase I projects are in the process of being awarded. One project (109) seeks to convert a mainframe morbidity/mortality surveillance program for microcomputer use. Another (24) proposes to design a PC software package for computing sample size and statistical power in clinical trials using simulations of time-to-event studies. The last (23) provides 3D visualization and mouse input facilities to the new PC version of the popular MLAB modeling program. The ongoing Phase II grants focus on software development. One investigator (132) is developing DC-CMAS, a user-friendly PC package for the analysis of food constituents and contaminants by integrating several comprehensive nutrition files into a single program. The second project (155) provides an invaluable cancer information resource for the PC by incorporating IARC's Directory of Ongoing Research in Cancer Epidemiology and monograph series along with a number of other useful databases onto CD-ROM, to be made accessible through a search module and indexing. The third Phase II grant (74) is supporting the development of a 3D graphics enhanced program (CAST) for detecting and describing cancer clusters in space and time. Several sophisticated statistical techniques are available within the package.

There were seven active SBIR contracts during FY-91. Three phase II contracts (208, 212, 213) involve development of electronic statistical tables, computed

probability values and function plotting based on the underlying algorithms. One investigator (213) split the project into two parallel efforts, delivering a marketable electronic table package at the end of Phase I. The coordinator is developing a statistical workbench for probing theoretical aspects of various widely-used distributions through a spreadsheet-like value-entry table. Four contracts concern genetic probes. One contractor (214) is working on a probe to detect the presence of the variant gene responsible for reduced metabolism of debrisoquine. Individuals with this variant are unable to correctly utilize certain medically important drugs. The second researcher (211) is mapping DNA markers located near the putative gene for hereditary melanoma on human chromosome 1p. Another two Phase I contracts include the purification of HTLV-2 antigen. Both investigators (210, 217) were working on isolating unique antigens from the envelope protein of HTLV-2 to develop specific antibodies that would not cross-react with HTLV-1. Such antibodies are important for screening blood products.

Projections:

Using figures from the President's Budget, NCI will spend approximately \$22.6 million on the SBIR program in FY-92. Phase I grant submissions are on the increase and showing an improved award rate. Approximately 30 new Phase I applications and 4 Phase II conversions are expected in the next year. The applications will, in all likelihood, be software-oriented and statistical in nature. Contract proposals will continue to fare better for Phase II conversion. The Branch proposes no new contract topics for the Omnibus Solicitation for FY-92. It is likely that at least two of the four terminating Phase I contracts will convert to Phase II funding. Although there have been indications that improvements in the length and amount of Phase I support as well as an increase in the mandatory set-aside are under consideration, nothing substantive has developed. Furthermore, SBIR renewal legislation has not yet progressed in Congress. Nevertheless, the Branch continues to foster the concept of the small business contribution to Federal research needs and technology transfer through commercialization.

EXTRAMURAL PROGRAMS BRANCH

GRANTS ACTIVE DURING FY 91

Investigator/Institution/Grant Number	Title
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1. ALLEN, Susan A. Univ. of California, San Francisco 5 R01 CA 50847-03	HIV, HPV -- Cancer in Rwanda
2. ANDERSON, David E. Univ. of Texas System Cancer Ctr. 5 R01 CA 29614-09	Genetics of Breast Cancer
3. ANDERSON, David E. Univ. of Texas System Cancer Ctr. 5 R01 CA 40173-05	Genetic Epidemiology of Male and Female Breast Cancer
4. ANDERSON, Harold D. Stephens College 1 R15 CA 41999-01A2	Trace-Element Nutrition & Cancer Etiology
5. ARMSTRONG, R. Warwick University of Illinois 5 R01 CA 46567-02	Nasopharyngeal Carcinoma and Dust and Smoke in Malaysia
6. AWERBACH, Tamara E. Harvard University 5 R01 CA 37820-06	Mathematics of Diffusion Assays--Mutagens & Antibiotics
7. BARTSCH, Helmut Int. Agency Res. Cancer 1 R13 CA 54157-01	Biomonitoring and Susceptibility Markers in Human Cancer
8. BECKER, David I.S. Grupe, Inc. 1 R43 CA 51554-01	Development of a Research Question Database
9. BECKER, Mark P. University of Michigan 5 R29 CA 53787-02	Analysis of Repeated Categorical Measurements
10. BECKER, Thomas M. University of New Mexico 5 R29 CA 48003-03	Epidemiology of Cervical Dysplasia in Minority Women
11. BEGG-MARINO, Lisa University of Pittsburgh 5 R01 CA 44751-02	Epidemiology of Obesity, Sex Hormones & Breast Cancer

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| 12. BERESFORD, Shirley A.
University of Washington
5 R01 CA 47749-03 | Endometrial Cancer Risk and
Post-Menopausal Hormone Use |
| 13. BERKOWITZ, Gertrud S.
Mt. Sinai Sch. Med.
5 R29 CA 47053-05 | Prevalence & Epidemiology
of Cryptorchidism |
| 14. BERNSTEIN, Leslie
University of Southern California
5 R01 CA 44546-05 | A Case-Control Study of
Cancer in Young Women |
| 15. BODIAN, Carol A.
Mt. Sinai Sch. Med.
7 R01 CA 46470-03 | Risk of Breast Cancer after
Proliferative Benign
Disease |
| 16. BOSL, George J.
Sloan-Kettering Institute
5 R01 CA 43074-05 | Statistical Methods for
Cancer Clinical Trials |
| 17. BOYD, Norman F.
Ontario Cancer Institute
5 R01 CA 48997-02 | Plasma Lipids and Familial
Breast Cancer |
| 18. BRADLOW, H. Leon
Institute for Hormone Research
7 R01 CA 39734-05 | Obesity, Diet, Estrogens
& Cancer Risk |
| 19. BRESLOW, Norman E.
University of Washington
5 R01 CA 40644-07 | Statistical Methods in
Cancer Epidemiology |
| 20. BRESLOW, Norman E.
Fred Hutchinson Cancer Res. Ctr.
1 R01 CA 54498-01 | Late Effects in Wilms'
Tumor Survivors and
Offspring |
| 21. BROOKMEYER, Ronald S.
Johns Hopkins University
2 R01 CA 48723-04A1 | Development/Application of
Statistical & Quantitative
Methods in AIDS Research |
| 22. BUCKLEY, Jonathan D.
University of Southern California
5 R01 CA 38908-05 | Epidemiology/Biology of
Childhood Non-Hodgkin's
Lymphoma |
| 23. BUNOW, Barry J.
Civilized Software, Inc.
1 R43 CA 52407-01A1 | MLAB 3D Graphics:
Scientific Visualization
Software |
| 24. BUNOW, Barry J.
Civilized Software, Inc.
1 R43 CA 54004-01 | Design Power Software
for Clinical Studies |

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| 25. BURT, Randall W.
University of Utah
5 R01 CA 40641-06 | Inheritance of Discrete
Colorectal Adematous Polyps |
| 26. CAMPBELL, T. Colin
Cornell University, Ithaca
5 P01 CA 33638-06 | Diet & Cancer in China |
| 27. CANNON-ALBRIGHT, Lisa A.
University of Utah
1 R03 CA 54936-01 | Analysis of Familial
Clustering of Cancer in
Utah |
| 28. CHU, Joseph
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 50795-02 | The Relationship of CIN III
& Human Papillomavirus |
| 29. COLDITZ, Graham
Brigham & Women's Hospital
5 R01 CA 46475-03 | Benign Breast Disease &
Risk of Breast Cancer |
| 30. COLTON, Theodore
Boston University
5 R01 CA 40240-05 | Breast Cancer Risk in Women
Given DES in Pregnancy |
| 31. COMSTOCK, George W.
Johns Hopkins University
5 R01 CA 36390-06 | Serologic Precursors of
Cancer |
| 32. COMSTOCK, George W.
Johns Hopkins University
5 R01 CA 47503-04 | Blood & Data Bank for
Cancer Risk Factor Studies |
| 33. CORREA, Pelayo
Louisiana State Univ. Med. Ctr.
2 P01 CA 28842-09 | Etiologic Studies of
Gastric Carcinoma |
| 34. CORREA, Pelayo
Louisiana State Univ. Med. Ctr.
5 R01 CA 40095-06 | Lung Cancer in Non-Smoking
Women |
| 35. CROUCH, Edmund A.
Tufts University
1 R01 CA 50726-01A1 | Analysis of the CBDS
Database |
| 36. DALING, Janet R.
Fred Hutchinson Cancer Res. Ctr.
1 R01 CA 52656-01A1 | The Changing Epidemiology
of Thyroid Cancer |
| 37. DE METS, David L.
University of Wisconsin, Madison
5 R01 CA 18332-17 | Statistical Problems in
Cancer Research |

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| 38. DUPONT, William D.
Vanderbilt University
5 R01 CA 46492-03 | Breast Cancer in Women with
Proliferative Breast
Disease |
| 39. DUPONT, William D.
Vanderbilt University
5 R01 CA 50468-02 | Epidemiology of Molecular
Risk Factors for Breast
Cancer |
| 40. EMERSON, Scott S.
University of Arizona
1 R29 CA 53449-01 | Group Sequential Methods
for Clinical Trials |
| 41. EZZIO, David J.
Yankee Software
1 R43 CA 53071-01 | Development of a New CATI
Package for Networked PCs |
| 42. FINKELSTEIN, Dianne M.
Massachusetts General Hospital
5 R01 CA 47048-03 | Carcinogenicity Experiments
for Environmental Health |
| 43. FISCHL, Margaret A.
University of Miami
4 R37 CA 34988-09 | Heterosexual & Household
Transmission of HTLV-III |
| 44. FOLSOM, Aaron R.
University of Minnesota
5 R01 CA 39742-07 | Distribution of Body Fat
& Cancer Risk in Women |
| 45. FRIEDMAN, Gary D.
Kaiser Foundation Res. Inst.
5 R37 CA 19939-13 | Drug Surveillance: Cancer
& Other Adverse Effects |
| 46. FRIEDMAN, Gary D.
Kaiser Foundation Res. Inst.
5 R01 CA 36074-05 | Are Low-Yield Cigarettes
Less Hazardous? |
| 47. FRIEDMAN, Gary D.
Kaiser Foundation Res. Inst.
5 R35 CA 49761-03 | Cancer Epidemiology in a
Large Health Care Plan |
| 48. GILL, Parkash S.
University of Southern California
5 R01 CA 51621-03 | Pathogenesis of Kaposi's
Sarcoma |
| 49. GLASER, Sally L.
Northern California Cancer Center
5 R29 CA 50381-03 | Reproductive Factors in
Hodgkin's Disease in Women |
| 50. GLYNN, Robert J.
Massachusetts Eye and Ear Infirmary
1 R03 CA 50546-01A2 | Objective Measure of
Sunlight Damage and
Epidemiology |

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| 51. GOLD, Ellen B.
University of California
5 R01 CA 50371-02 | Family History in Children
with Brain Tumors |
| 52. GORBACH, Sherwood L.
Tufts University
5 R37 CA 45128-06 | Diet, Estrogens, & Breast
Cancer |
| 53. GRAHAM, Saxon
State University of New York, Buffalo
5 P01 CA 11535-19 | Social Epidemiology of
Cancer |
| 54. GREENHOUSE, Joel B.
Carnegie Mellon University
1 R01 CA 54852-01 | Bayesian Methods in
Biostatistics |
| 55. GROOPMAN, John D.
Johns Hopkins University
5 U01 CA 48409-04 | Monitoring Human Exposure
to Aflatoxins in the Gambia |
| 56. GROOPMAN, John D.
Johns Hopkins University
5 R01 CA 54114-02 | Aflatoxin DNA Adducts
Detected by Monoclonal
Antibodies |
| 57. GRUFFERMAN, Seymour
University of Pittsburgh
5 R01 CA 21244-08 | The Epidemiology of
Childhood Rhabdomyosarcoma |
| 58. GRUFFERMAN, Seymour
University of Pittsburgh
5 R01 CA 47473-04 | Case-Control Study of
Hodgkin's Disease in
Childhood |
| 59. GRUFFERMAN, Seymour
University of Pittsburgh
5 R01 CA 48643-03 | Epidemiologic Studies of
HIV-Associated Malignancies |
| 60. HAILE, Robert W.
Univ. of California, Los Angeles
5 R01 CA 36387-08 | Genetic-Epidemiologic Study
of Bilateral Breast Cancer |
| 61. HAILE, Robert W.
Univ. of California, Los Angeles
1 R01 CA 51923-01A1 | Sigmoidoscopy Based Case
Control Study of Polyps |
| 62. HANASH, Samir M.
University of Michigan, Ann Arbor
5 P01 CA 26803-11 | Program Project: The Study
of Human Mutation |
| 63. HARRINGTON, David P.
Dana-Farber Cancer Institute
2 R01 CA 39929-07 | Nonparametric Statistical
Tests for Censored Cancer
Data |

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| 64. | HERTZ-PICCIOTO, Irva
Univ. of North Carolina, Chapel Hill
1 R03 CA 53637-01 | The Healthy Worker Survivor
Effect & Cancer Mortality |
| 65. | HJELLE, Brian L.
University of New Mexico
1 R01 CA 55480-01 | Prevalence & Pathologic
Burden of HTLV-2 Infection |
| 66. | HOLFORD, Theodore R.
Yale University
5 R01 CA 30931-10 | Systematic Analysis:
Connecticut Cancer
Incidence Trends |
| 67. | HOLLY, Elizabeth A.
Northern California Cancer Ctr.
5 R01 CA 42440-03 | Mutagenic Mucus in the
Uterine Cervix of Smokers |
| 68. | HOLLY, Elizabeth A.
Northern California Cancer Ctr.
5 R01 CA 45614-04 | Epidemiology of Non-
Hodgkin's Lymphoma and
Retroviral Tests |
| 69. | HOLMES, King K.
University of Washington
5 R01 CA 34493-08 | Etiology & Natural History
of Cervical Neoplasia |
| 70. | HORN, Pamela L.
Northern California Cancer Ctr.
5 R29 CA 49499-02 | Epidemiology of Salivary
Gland Cancer |
| 71. | HSIEH, Chung-Cheng
Harvard School of Public Health
5 R01 CA 44683-03 | Case-Control Study of
Cancer of the Extrahepatic
Bile Duct |
| 72. | HSU, Jason C.
Ohio State University
5 R01 CA 41168-04 | Multiple Comparisons with
the Best Treatment |
| 73. | HULKA, Barbara S.
University of North Carolina
5 R03 CA 52447-02 | Rare HA-RAS Alleles and
and Breast Cancer |
| 74. | JACQUEZ, Geoffrey M.
Applied Biomathematics, Inc.
2 R44 CA 50800-02 | Statistical Detection
of Cancer Clusters |
| 75. | JANGHORBANI, Morteza
University of Chicago
5 R01 CA 38943-06 | Assessment of Selenium
Status in Man |
| 76. | JENSEN, Ole M.
Danish Cancer Registry
5 R01 CA 47812-02 | Human Papillomavirus and
Cervical Cancer in
Copenhagen |

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| 77. JENSEN, Ronald H.
Lawrence Livermore National Lab.
5 U01 CA 48518-03 | Glycophorin A-Based Assay
of Somatic Cell Mutations |
| 78. JONES, Michael P.
University of Iowa
1 R29 CA 55212-01 | Survival Analysis for
Cancer Data |
| 79. KALOW, Werner
University of Toronto
5 U01 CA 48354-03 | Caffeine Metabolic Ratios
Serving Epidemiology |
| 80. KATZ, Ben Z.
Yale University
5 R01 CA 48270-03 | EBV-Associated Lympho-
proliferations in AIDS |
| 81. KELSEY, Jennifer L.
Columbia University
5 R03 CA 52107-02 | Random Digit Dailing:
An Evaluation |
| 82. KIM, Kyungmann
Dana-Farber Cancer Institute
5 R29 CA 52733-02 | Sequential Methods for
Clinical Trials |
| 83. KING, Mary C.
Univ. of California, Berkeley
5 R01 CA 27632-11 | Genetic Epidemiology |
| 84. KIVIAT, Nancy
Harborview Medical Center
5 R01 CA 50738-03 | Epidemiology of Anal
Dysplasia in HIV Positive
& Negative Men |
| 85. KIVIAT, Nancy
University of Washington
5 R01 CA 50856-02 | Cervical Neoplasia and
HIV Infection in Senegal |
| 86. KOEHLER, Kenneth J.
Iowa State Univ. of Sci. & Tech.
1 R01 CA 51831-01A1 | Statistical Methods for
Correlated Survival Data |
| 87. KOLONEL, Laurence N.
University of Hawaii, Manoa
5 P01 CA 33619-09 | Epidemiologic Studies of
Diet & Cancer in Hawaii |
| 88. KOZIOL, James A.
Scripps Clinic & Res. Fdn.
2 R01 CA 41582-06 | Topics in Biostatistics |
| 89. KUEHL, Robert O.
University of Arizona
1 R13 CA 51709-01 | Fifteenth International
Biometric Conference |

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| 90. | LAGAKOS, Stephen W.
Harvard University
5 R01 CA 33041-09 | Biostatistical Methods for
Carcinogenicity Experiments |
| 91. | LAGAKOS, Stephen W.
Dana-Farber Cancer Institute
5 R01 CA 39640-07 | Biostatistical Problems in
Cancer Research |
| 92. | LAN, K.K. Gordon
George Washington University
1 R01 CA 55098-01 | Statistical Methods for
Cancer Clinical Trials |
| 93. | LE MARCHAND, Loic
University of Hawaii, Manoa
5 R29 CA 44503-04 | Body Weight in Youth &
Middle Age as Predictors
of Cancer |
| 94. | LE MARCHAND, Loic
University of Hawaii, Honolulu
5 R03 CA 52505-02 | Breath Markers of Colonic
Fermentation |
| 95. | LEVINE, Alexandra M.
University of Southern California
5 R01 CA 50850-03 | Epidemiology of HIV-Related
Lymphoma |
| 96. | LIVINGSTON, Gordon K.
University of Cincinnati
5 U01 CA 48429-03 | Micronuclei (DNA Lesions)
as Markers of Human
Exposure |
| 97. | LONDON, W. Thomas
Fox Chase Cancer Center
5 P01 CA 40737-06 | Hepatitis B Virus & Primary
Hepatocellular Carcinoma |
| 98. | LYNCH, Henry T.
Creighton University
5 R01 CA 47429-03 | Gene Probes in the FAMM |
| 99. | MACK, Thomas M.
University of Southern California
5 R35 CA 42581-06 | Epidemiologic Research in
Cancer Etiology |
| 100. | MACMAHON, Brian
Harvard University
5 R01 CA 47305-04 | Alcohol Consumption,
Lactation, & Breast Cancer
Risk |
| 101. | MAKUCH, Robert W.
Yale University
5 R03 CA 50287-02 | Analysis of Repeated T4
Data to Predict KS Risk |
| 102. | MARGO, Richard A.
Margo & Associates
1 R43 CA 53073-01 | A Global, Integrated
Modular Clinical Trial
System |

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| 103. | MARSHALL, James R.
State Univ. of New York, Buffalo
1 R13 CA 54182-01 | Symposium on Future
Directions of Diet & Cancer |
| 104. | MC DOUGALL, James K.
Fred Hutchinson Cancer Res. Ctr.
5 P01 CA 42792-05 | HPV: Biology, Clinical
Significance &
Epidemiology |
| 105. | MC GLYNN, Katherine A.
Fox Chase Cancer Center
5 R03 CA 48798-02 | Smoking, Hepatitis B Viral
Replication and Liver
Damage |
| 106. | MC GLYNN, Katherine A.
Fox Chase Cancer Center
5 R03 CA 51877-02 | Cancer Morbidity and
Mortality in Blood Donors |
| 107. | MEHTA, Cyrus R.
Dana-Farber Cancer Institute
2 R01 CA 33019-09 | Statistical Methods for
Cancer Treatment &
Prevention |
| 108. | MILLER, Kenneth J.
Rensselaer Polytechnic Inst.
5 R01 CA 28924-06 | Computer Assisted Analysis
of Carcinogenicity |
| 109. | MITCHELL, Herman E.
New England Research Institute
1 R43 CA 53068-01A1 | Microcomputer Mortality
Surveillance System |
| 110. | MODAN, Baruch
Chaim Sheba Medical Center
5 R01 CA 51117-02 | Brain Tumors & N-Nitroso
Exposures |
| 111. | MONSON, Richard R.
Harvard University
5 R01 CA 22849-13 | Second Cancers in Patients
with Hodgkin's Disease |
| 112. | MOOLGAVKAR, Suresh H.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 47658-04 | Biomathematical Approaches
to Cancer |
| 113. | MOSCICKI, Barbara
University of California
5 R01 CA 51323-02 | Natural History of HPV in
Teens: Infection to
Neoplasia |
| 114. | MUELLER, Nancy E.
Harvard University
5 R37 CA 38450-06 | Natural History of HTLV-1
Infection |
| 115. | MUELLER, Nancy E.
Harvard University
5 R01 CA 44578-04 | The Epidemiology of
"Classic" Kaposi's Sarcoma |

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| 116. | NAGAMANI, Manubai
University of Texas Med. Br.
5 R01 CA 45181-03 | Ovarian Steroids in
Endometrial Cancer during
Menopause |
| 117. | NEWCOMB, Polly Ann
Univ. of Wisconsin Clin. Cancer Ctr.
5 R01 CA 47147-04 | Alcohol Consumption,
Lactation, & Breast Cancer
Risk |
| 118. | NOMURA, Abraham M.
Kuakini Medical Center
5 R01 CA 33644-09 | Cancer Epidemiology of the
Migrant Japanese in Hawaii |
| 119. | O'BRIEN, Peter C.
Mayo Foundation
5 R01 CA 36873-05 | In Utero DES Exposure:
Cancer & Medical Illnesses |
| 120. | O'NEILL, Ian K.
Int. Agency Res. Cancer
5 R01 CA 39417-05 | In Vivo Microcapsule
Monitoring of Carcinogens |
| 121. | OAKES, David
University of Rochester
5 R01 CA 52572-02 | Statistical Analysis of
Multiple Event Time Data |
| 122. | OLSHAN, Andrew F.
University of Pittsburgh
1 R01 CA 53583-01 | A Case-Control Study of
Risk Factors for
Neuroblastoma |
| 123. | OLSHEN, Richard A.
Stanford University
1 R01 CA 55325-01 | Tree-Structured Statistical
Methods |
| 124. | PAFFENBARGER, Ralph S.
Stanford University
5 R01 CA 44854-03 | Physical Activity, Body
Size, & Cancer Incidence |
| 125. | PAFFENBARGER, Ralph S.
Stanford University
5 R01 CA 49446-03 | Prostate Cancer in High,
Medium and Low-Risk
Populations |
| 126. | PAGANINI-HILL, Annlia
University of Southern California
5 R01 CA 32197-10 | Estrogens & Vitamin: A Role
in Disease Prevention |
| 127. | PALEFSKY, Joel M.
University of California
1 R01 CA 54053-01A1 | Natural History of Anal
Neoplasia in HIV-Infected
Men |
| 128. | PALMER, Julie
Boston University
5 R01 CA 52223-02 | Gestational Trophoblastic
Disease & Oral
Contraceptives |

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| 129. | PASTERNAK, Bernard S.
New York University
5 R01 CA 34588-07 | Endocrine & Environmental
Factors in Breast Cancer
Human Subjects |
| 130. | PERERA, Frederica P.
Columbia University
5 R01 CA 51196-02 | Biomarkers of Environmental
Tobacco Smoke Exposure |
| 131. | PETERS, Ruth K.
University of Southern California
5 R01 CA 44401-05 | Case-Control Study of
Adenocarcinoma of the
Cervix |
| 132. | PETERSEN, Barbara J.
Technical Assessment Systems, Inc.
2 R44 CA 50045-02 | Dietary Constituent Cancer
Modulation Analysis System |
| 133. | PETRAKIS, Nicholas
Univ. of California, San Francisco
5 P01 CA 13556-18 | Epidemiology & Natural
History of Breast Cancer |
| 134. | PETRAKIS, Nicholas
Univ. of California, San Francisco
5 R01 CA 47288-03 | Breast Cancer Incidence in
Women with Abnormal Breast
Cytology |
| 135. | PIERCE, Donald A.
Oregon State University
5 R01 CA 51007-02 | Statistical Analysis of
Cancer in Atomic Bomb
Survivors |
| 136. | PIKE, Malcolm C.
University of Southern California
5 R01 CA 48774-03 | A Case-Control Study of
Post-Menopausal Endometrial
Cancer |
| 137. | PRENTICE, Ross
Fred Hutchinson Cancer Res. Ctr.
9 P01 CA 53996-14 | Statistical Methods for
Medical Studies |
| 138. | PRESTON-MARTIN, Susan
University of Southern California
5 R01 CA 47082-04 | Childhood Brain Tumors &
N-Nitroso Exposures: U.S.
Studies |
| 139. | RAGNI, Margaret V.
University of Pittsburgh
5 R01 CA 50849-03 | Study of HIV-Associated
Malignancy in Hemophiliacs |
| 140. | RANDALL, D. Elizabeth
State University of New York, Buffalo
5 R03 CA 51720-02 | Dietary Patterns & Cancer |
| 141. | RICE, John A.
University of California, San Diego
5 R01 CA 41628-06 | Biostatistics: Modeling
and Inference |

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| 142. | ROBISON, Leslie L.
Univ. of Minnesota, Mnpls-St.Paul
5 R01 CA 48051-04 | Epidemiology of Childhood
Acute Lymphoblastic
Leukemia |
| 143. | ROBISON, Leslie L.
Univ. of Minnesota, Mnpls-St.Paul
5 R01 CA 49450-03 | Acute Nonlymphoblastic
Leukemia in Children |
| 144. | ROSENBERG, Lynn
Boston University Sch. Med.
5 R37 CA 45762-04 | Case-Control Surveillance
of Serious Illnesses &
Drugs |
| 145. | ROSNER, Bernard A.
Brigham & Women's Hospital
5 R01 CA 50597-03 | Measurement Errors in
Cancer & Respiratory
Epidemiology |
| 146. | ROSS, Ronald K.
University of Southern California
5 P01 CA 17054-16 | USC Cancer Center
Epidemiology and
Biostatistics Unit |
| 147. | ROSS, Ronald K.
University of Southern California
5 R01 CA 36388-05 | Case-Control Study of
Multiple Myeloma |
| 148. | ROSS, Ronald K.
University of Southern California
5 R01 CA 43092-05 | Dietary Factors in the
Etiology of Cancer |
| 149. | ROUSH, George C.
New York University Med. Ctr.
5 R03 CA 52414-02 | Enzymatic Measures of
Oxidative Stress and
Breast Cancer |
| 150. | RYAN, Louise
Dana-Farber Cancer Institute
5 R29 CA 48061-04 | Biostatistical Topics in
Carcinogenicity &
Teratology |
| 151. | SANDLER, Robert S.
University of North Carolina
5 R01 CA 44684-04 | Risk Factors for Colon
Adenomas |
| 152. | SAUNDERS, L. Duncan
California Public Health Fdn.
5 R01 CA 48288-03 | AIDS & Cancer--New Insights
Through Record Linkage |
| 153. | SAVITZ, David A.
Univ. of North Carolina, Chapel Hill
5 R03 CA 48908-02 | Menstrual Cycle Patterns
& Risk of Breast Cancer |
| 154. | SCHANTZ, Stimson P.
M.D. Anderson Cancer Center
1 R01 CA 51845-01A1 | Multiple Primary Cancers
& Mutagen Hypersensitivity |

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| 155. | SCHIPMA, Peter B.
I.S. Grupe, Inc.
2 R44 CA 50842-02A1 | Epidemiology Information
Resource on Optical Disk |
| 156. | SCHLESSELMAN, James J.
Henry M. Jackson Foundation
5 R01 CA 50193-03 | Oral Contraceptives &
Cancer |
| 157. | SCHOTTENFELD, David
University of Michigan, Ann Arbor
1 R03 CA 54119-01 | COPD as a Risk Factor
for Lung Cancer |
| 158. | SCHWARTZ, Ann G.
Michigan Cancer Foundation
5 R29 CA 50383-02 | Familial Risk of Lung
Cancer |
| 159. | SHAH, Keerti V.
Johns Hopkins University
1 R03 CA 52543-01 | HPV Diagnosis by PCR in
in Cervical Cancer Studies |
| 160. | SHERMAN, Karen J.
Fred Hutchinson Cancer Res. Ctr.
1 R01 CA 48996-01A2 | Oral Cancer--Epidemiology/
Biochemistry/Immunology |
| 161. | SHORE, Roy E.
New York University
5 R37 CA 43175-06 | Follow-Up of Patients
X-Irradiated for Scalp
Ringworm |
| 162. | SHUKER, David E. G.
Int. Agency Res. Cancer
5 U01 CA 48473-03 | Excreted Alkyl Purines as
Markers of <u>in vivo</u> DNA
Damage |
| 163. | SHY, Carl M.
University of North Carolina
1 R03 CA 53193-01 | Health Effects of
Chlorinated Water |
| 164. | SKOLNICK, Mark H.
University of Utah
5 R01 CA 36362-08 | Linkage Analysis and
Multiple Loci |
| 165. | SKOLNICK, Mark H.
University of Utah
5 P01 CA 48711-02 | Genetic Epidemiology of
Cancer & Predisposing
Lesions |
| 166. | SLATTERY, Martha L.
University of Utah
1 R01 CA 48998-01A2 | Diet, Activity, and
Reproduction as Risks
for Colon Cancer |
| 167. | SPEIZER, Frank E.
Brigham & Women's Hospital
5 R37 CA 40356-07 | Prospective Study of Diet
& Cancer in Women |

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| 168. | SPEIZER, Frank E.
Brigham & Women's Hospital
5 R01 CA 49449-03 | Biochemical Markers in the
Nurses' Health Study Cohort |
| 169. | SPITZ, Margaret R.
Univ. of Texas System Cancer Ctr.
5 R03 CA 50945-02 | Environmental & Genetic
Interactions in Risk of
Aerodigestive Tract Cancer |
| 170. | STETTER, Joseph R.
Transducer Research, Inc.
1 R43 CA 50009-01A1 | Simple Measurement of
Carbon Monoxide on the
Breath |
| 171. | STEWART, Clinton F.
University of Tennessee
5 R03 CA 52745-02 | Racial Differences in
Hepatic Metabolism and
Cancer Risk |
| 172. | STOCKWELL, Heather G.
University of South Florida
5 R29 CA 45513-05 | Epidemiology of Lung Cancer
in Non-Smoking Women |
| 173. | STORER, Barry E.
University of Wisconsin
5 R29 CA 45313-04 | Biostatistical Methods for
Cancer Research |
| 174. | STRONG, Louise C.
University of Texas System Cancer Ctr.
5 P01 CA 34936-08 | A Mutational Model for
Childhood Cancer |
| 175. | STRONG, Louise C.
University of Texas System Cancer Ctr.
5 R01 CA 38929-07 | Genetic Epidemiology of
Childhood Sarcoma |
| 176. | STUKEL, Theresa
Dartmouth College
1 R01 CA 52192-01A1 | Tumor Growth Curve Analysis |
| 177. | SWIFT, Michael R.
University of North Carolina
5 R01 CA 14235-18 | Neoplasia-Predisposing
Genes of Man |
| 178. | SWIFT, Michael R.
University of North Carolina
5 R01 CA 50489-02 | Cancer Risk of Ataxia-
Telangiectasia
Heterozygotes |
| 179. | TANNER, Martin A.
University of Rochester
5 R01 CA 35464-08 | Nonparametric Analysis of
Censored Data |
| 180. | THOMAS, David B.
Fred Hutchinson Cancer Res. Ctr.
5 R37 CA 41530-06 | Trace Elements & Cancers
of Larynx, Esophagus &
Mouth |

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| 181. THOMAS, David B.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 49044-02 | Papilloma Viruses and
Cervical Cancer in Bangkok |
| 182. THOMAS, Duncan C.
University of Southern California
5 R01 CA 42949-05 | Time-Related Factors in
Cancer Epidemiology |
| 183. THOMAS, Duncan C.
University of Southern California
1 R01 CA 52862-01A1 | Survival Model for Genetic
Epidemiology |
| 184. TREVISAN, Maurizio
State Univ. of New York, Buffalo
5 R03 CA 49426-02 | A Diet Instrument for a
Population with Varied
Intakes |
| 185. TSIATIS, Anastasios A.
Dana-Farber Cancer Institute
5 R01 CA 51962-02 | Statistical Analysis of
Time to Event Data in
Cancer |
| 186. VALANIS, Barbara G.
Kaiser Foundation Hospitals
5 R01 CA 47727-03 | Health & Occupational
Exposure to Anti-Cancer
Drugs |
| 187. VANDERLAAN, Martin
Lawrence Livermore Natl. Lab.
5 U01 CA 48446-03 | Biochemical Measures of
Exposure to Dietary
Carcinogens |
| 188. VAUGHAN, Thomas L.
Fred Hutchinson Cancer Res. Ctr.
5 R29 CA 46552-04 | An Epidemiological Study
of Nasopharyngeal Cancer |
| 189. VAUGHAN, Thomas L.
Fred Hutchinson Cancer Res. Ctr.
5 R03 CA 50256-02 | Epidemiologic Study of
HLA Type & Nasopharyngeal
Cancer |
| 190. VINEIS, Paolo
University of Torino
1 R01 CA 51086-01A2 | Hematolymphopoietic
Malignancies in Italy |
| 191. WANG, Helen H.
Beth Israel Hospital
5 R03 CA 48744-03 | Epidemiology of
Lymphomatoid Papulosis |
| 192. WEI, Lee-Jen
University of Wisconsin, Madison
5 R01 CA 45544-04 | Nonparametric Statistical
Methods in Cancer Research |
| 193. WEI, Lee-Jen
University of Wisconsin, Madison
1 R01 CA 53546-01A1 | Statistical Semi-Parametric
Method for Cancer Studies |

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| 194. | WEINSTOCK, Martin A.
Roger Williams General Hospital
5 R29 CA 49531-02 | A Case-Control Study of
Dysplastic Nevi |
| 195. | WEISS, Noel S.
University of Washington
5 R35 CA 39779-07 | Research in Cancer
Epidemiology |
| 196. | WESTHOFF, Carolyn L.
Columbia University
1 R01 CA 50658-01A2 | Case-Control Study of
Benign Ovarian Neoplasms |
| 197. | WHITE, Emily
Fred Hutchinson Cancer Res. Ctr.
5 R29 CA 44790-05 | Epidemiology of Physical
Activity & Colon Cancer |
| 198. | WHITTEMORE, Alice S.
Stanford University
5 R35 CA 47448-03 | Research in Cancer
Epidemiology and
Biostatistics |
| 199. | WILLETT, Walter C.
Harvard School of Public Health
5 R01 CA 50385-03 | Risk Factors for Breast
Cancer Among Young Nurses |
| 200. | WILLETT, Walter C.
Brigham & Women's Hospital
5 R03 CA 51185-02 | A Prospective Study of
Diet & Colorectal Adenomas |
| 201. | WILLETT, Walter C.
Harvard School of Public Health
1 P01 CA 55075-01 | Prospective Studies of Diet
& Cancer in Men & Women |
| 202. | WOOLSON, Robert F.
University of Iowa
5 R01 CA 39065-06 | Epidemiologic Methods for
Case-Control/Ecologic
Studies |
| 203. | WRENSCH, Margaret R.
University of California
1 R01 CA 52689-01A1 | Genetic Epidemiology of
Malignant Glioma |
| 204. | WYNDER, Ernst L.
American Health Foundation
5 P01 CA 32617-08 | Interdisciplinary Studies
in Cancer Epidemiology |
| 205. | YU, Mimi C.
University of Southern California
5 R01 40468-06 | Salted Fish &
Nasopharyngeal Carcinoma |
| 206. | ZELEN, Marvin
Dana-Farber Cancer Institute
5 R01 CA 23415-12 | Statistical Models of
Biomedical Phenomena |

207. ZIMMERMAN, Stuart O. Biomathematics & Computing
Univ. of Texas System Cancer Ctr. in a Cancer Institute
5 R01 CA 11430-25

CONTRACTS ACTIVE DURING FY 91

Investigator/Institution/Contract -----	Title -----
208. BATTISTE, E. C. C. Abaci, Inc. N44 CP 05729	Scientific Distribution Function Software for Biostatistical Operation
209. DETELS, Roger University of California, Los Angeles N01 AI 32511	Natural History of AIDS in Homosexual Men
210. DOLBY, Nichol Hawaii Biotechnology Group, Inc. N43 CP 05695	Cloning & Expression of Recombinant HTLV-II Envelope Protein in <u>E. coli</u>
211. KLINGER, Katherine W. Integrated Genetics N43 CP 05693	High Resolution Mapping of Distal Chromosome 1p
212. MAULUCCI, Ruth A. MOCO, Inc. N44 CP 05639	Microcomputer Generated Statistical Tables
213. MEHTA, Cyrus R. Cytel Software Corp. N44 CP 05727	Electronic Tables for Statisticians
214. MOIR, Donald T. Collaborative Research, Inc. N43 CP 05694	A DNA Probe Test for Debrisoquine Hydroxylase Phenotype
215. RINALDO, Charles R., Jr. University of Pittsburgh N01 AI 32513	Natural History of AIDS in Homosexual Men
216. SAAH, Alfred Johns Hopkins University N01 AI 32520	Natural History of AIDS in Homosexual Men
217. STABINSKY, Yitzhak TBC Research Laboratories N43 CP 05696	Production of Recombinant HTLV-2 Envelope Protein in <u>E. coli</u>

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